The Synthesis of Some Pyrrole-containing Marine Natural Products

A thesis submitted for the degree of Doctor of Philosophy
at the Australian National University

by

Katrin Hasse

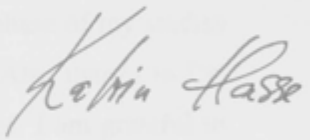
Research School of Chemistry
Canberra, Australia

June, 2011

To My Parents

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me, during the period 2006-2010 and has not been previously presented for the examination of any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they were derived.



Katrin Hasse

June, 2011

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Table of Contents

Table of Contents 1

Abstract 4

Publications and Conference Contributions Based on Work Carried out During the Period of PhD Candidature 7

Glossary 8

Chapter One: ***Introduction to Marine Alkaloids and Natural Product Synthesis***

Index to Chapter 1 11

1.1 Natural Products from Marine Organisms 12

1.2 The Purpose of Natural Product Synthesis 13

1.3 Lamellarins and Related Pyrrolic Alkaloids Derived from Marine Organisms 14

1.3.1 The Lamellarin Family of Marine Alkaloids 14

1.3.1.1 Occurrence and Structural Elucidation 14

1.3.1.2 Proposed Biogenesis of the Lamellarins 18

1.3.1.3 Biological Activity 18

1.3.2 The Ningalins Family of Marine Alkaloids 21

1.3.2.1 Occurrence and Structural Elucidation 21

1.3.2.2 Biological Activity 22

1.3.3 Structural Comparison of the Lamellarins with Ningalin B 23

1.4 References 24

Chapter Two: ***A Total Synthesis of the Marine Alkaloid Ningalin B from (S)-Proline***

Index to Chapter 2 26

2.1 Previous Syntheses of Ningalin B 28

2.2 Retrosynthetic Analysis of Ningalin B 34

2.3 Results and Discussion 35
1.3.1 Early Stages Associated with the Synthesis of Ningalin B 35
1.3.2 Synthesis of the Boronic Ester Coupling Partner **45** 38
1.3.3 Completion of the Synthesis of Ningalin B 39
2.4 Summary and Conclusions 46
2.5 References 48

Chapter Three: ***Synthetic Investigations into the Biogenesis of the Pentacyclic Lamellarin Framework***

Index to Chapter 3 49
3.1 Previous Approaches Used in Assembling the Pentacyclic Lamellarin Framework 51
3.2 First Generation Approach to Lamellarin G Trimethyl Ether 60
3.2.1 Retrosynthetic Analysis 60
3.2.2 Results and Discussion 61
3.2.3 An Unusual Ring-closing Reaction and its Implications for Mimicking the Biogenesis of the Pentacyclic Lamellarins 63
3.3 Second Generation Approach to Lamellarin G Trimethyl Ether 65
3.3.1 Retrosynthetic Analysis 65
3.3.2 Results and Discussion 67
3.4 Summary and Conclusions 79
3.5 References 80

Chapter Four: ***Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S***

Index to Chapter 4 81
4.1 Introduction to Lamellarin S 82
4.2 Modular Total Synthesis of Lamellarin G Trimethyl Ether 83
4.2.1 Retrosynthetic Analysis (Third Generation Approach) 85
4.2.2 Results and Discussion 86
4.2.3 Summary and Conclusion 89
4.3 Modular Total Synthesis of Lamellarin S 90

4.3.1 Retrosynthetic Analysis 90
4.3.2 Preparation of Building Blocks **125**, **126** and **127** Required for the Synthesis of Lamellarin S 91
4.3.3 Completion of the Total Synthesis of Lamellarin S 93
4.4 Conclusions 97
4.5 References 98

Chapter Five: ***Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S***

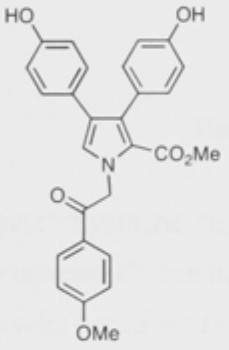
Index to Chapter 5 99
5.1 General Procedures 100
5.2 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 2 102
5.3 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 3 119
5.4 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 4 137
5.5 References 159

Appendices

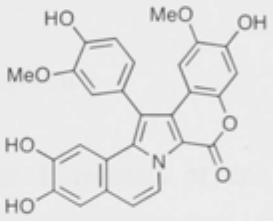
Index to Appendices 160
Crystallographic Studies Associated with Compounds in Chapter 2 161
Crystallographic Studies Associated with Compounds in Chapter 3 176

Abstract

Chapter One; "Introduction to Marine Alkaloids and Natural Product Synthesis", provides a brief introduction on the general properties of marine alkaloids and why chemists pursue the synthesis of such natural products. Certain members of the lamillarin family of marine alkaloids exhibit potent cytotoxic activities and a capacity to inhibit HIV-integrase. As such, they are interesting targets for total synthesis. The first half of Chapter One is a short review and discusses the structural diversity of the lamellarin familiy (examples of which are shown in Figure I), the proposed biosynthetic origins and the most prominent biological activities within this group of compounds.



Lamellarin O



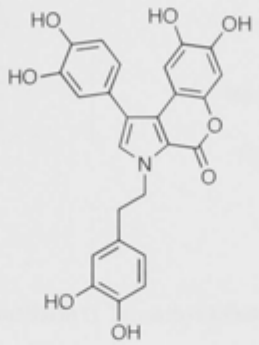
Lamellarin D

Figure I: Structures of Represantitive Members of the Lamellarin Family of Marine Alkaloids

Certain members of the ningalin family of marine alkaloids have the ability to reverse multi-drug resistance (MDR) at nontoxic concentrations and, therefore, are equally interesting synthetic targets. The second half of Chapter One introduces the ningalin family of marine alkaloids and discusses the structural diversity and the most prominent biological activities for these compounds. Chapter One finishes with a structural comparison between these two families of marine alkaloids.

Chapter Two; "A Total Synthesis of the Marine Alkaloid Ningalin B from (*S*)-Proline", commences with a discussion of previous total syntheses of ningalin B (**7**, Figure II). A possible new approach towards this natural product from (*S*)-proline is

then presented. A model study was used to demonstrate the validity of certain key reactions and to verify the proposed regioselective outcome within the reaction sequence. The results of this model study were then adapted to the completion of the total synthesis of ningalin B.



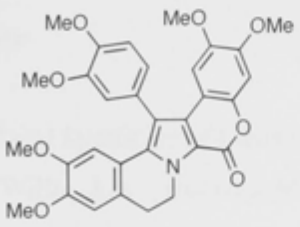
7

Figure II: Structure of Ningalin B

Chapter Three; "Synthetic Investigations into the Biogenesis of the Pentacyclic Lamellarin Framework", commences with the discussion of some previous syntheses of the pentacyclic lamellarin framework. Initial efforts to establish a new synthesis of the lamellarin G trimethyl ether (**55**, Figure III) using the intermediates formed in the course of preparing ningalin B led to some unexpected outcomes. While thwarting the original plans, these novel reactions prompted the idea that a biomimetic synthesis of the lamellarin framework could be established. Studies of this possibility led to a new approach to key intermediates in the synthesis of the lamellarins and, in due course, established new methodologies connected with general manipulations of compounds containing a pyrrole moiety. Despite these successes, an attempt to mimic key-bond-forming steps associated with the proposed biogenesis of the pentacyclic lamellarins failed.

Chapter Four; "Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S", focuses on the application of methodology developed in the preceeding Chapter to the establishment of a total synthesis of lamellarin G trimethyl ether (**55**). This was ultimately achieved and the modular nature of the established

synthesis provided a pathway to previously inaccessible members of the lamellarin family. This resulted in the first reported total synthesis of the racemic modification of lamellarin S (**120**, Figure III).



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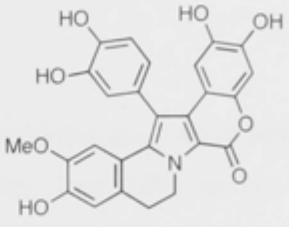

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Figure III: Structures of Lamellarin G Trimethyl Ether (**55**) and Lamellarin S (**120**)

Chapter Five contains the experimental procedures and characterisation data associated with the new compounds described in Chapters Two to Four.

Publications and Conference Contributions Based on Work Carried out During the Period of PhD Candidature

Publications

"Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S"
Hasse, K.; Willis, A. C.; Banwell, M. G.; *Eur. J. Org. Chem.* **2011**, 88-99.

"A Total Synthesis of Ningalin B from (*S*)-Proline"
Hasse, K.; Willis, A. C.; Banwell, M. G.; *Aust. J. Chem.* **2009**, *62*, 7, 683-691.

"Attempts to mimic key bond-forming events associated with the proposed biogenesis of the pentacyclic lamellarins"
Axford, L. C.; Holden, K. E.; Hasse, K.; Banwell, M. G.; Steglich, W.; Wagler, J.; Willis, A. C. *Aust. J. Chem.* **2008**, *61*, 2, 80-93.

Conference Contributions

23rd RACI Organic Chemistry Conference "Organic08"
Hobart, Australia, December 2008
Oral presentation entitled "Synthetic Investigations into the Pentacyclic Lamellarin Framework"

29th Annual One-Day Symposium, RACI, NSW Organic Chemistry Group
Sydney, Australia, December 2008
Poster presentation entitled "A Total Synthesis of Ningalin B from (*S*)-Proline"

5th SINO-Australia Organic Chemistry Symposium
Canberra, Australia, October 2008
Poster presentation entitled "A Total Synthesis of Ningalin B from (*S*)-Proline"

Glossary

Å	Angstrom
Ac	acetyl
AcOH	acetic acid
aq.	aqueous
BF_3•Et_2O	boron trifluoride diethyl etherate
Bn	benzyl
Boc	*tert*-butyloxy carbonyl
Bu	butyl
ca.	*circa* (approximately)
cat.	catalyst
conc.	concentrated
δ	chemical shift (parts per million)
DAD	diode-array detection
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMA	dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
E	*entgegen* (apart or opposite)
EI	electron impact
ESI	electrospray ionisation
Et	ethyl
eq.	equivalents
eV	electron volt
e. g.	*exempli gratia* (for example)
GI_{50}	Growth inhibitor (the concentration that causes 50% growth inhibition)
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i. e.	*id est* (that is)
INEPT	insensitive nuclei enhanced by polarisation transfer
IR	infrared
i-Pr	*iso*-propyl
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
lit.	literature
μ-wave	microwave
M	molar
$M^{+\bullet}$	molecular ion
Me	methyl
MHz	Mega-Hertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point (°C)
m/z	mass-to-charge ratio
ν_{max}	infrared absorption maxima (cm^{-1})
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
Ref.	reference
R_f	retardation factor
R_t	retention time
sat.	saturated
SET	single electron transfer

TBAB	tetra-*n*-butylammonium bromide
THP	tetrahydro-2*H*-pranyl
t-Bu	*tertiary*-butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid / trifluoroacetate
Ts	*p*-toluenesulfonyl / tosyl
THF	tetrahydrofuran
v	volume
viz.	*videlicit* (namely)
wt	weight
Z	*zusammen* (together)

1 Introduction to Marine Alkaloids and Natural Product Synthesis

1.1 Natural Products from Marine Organisms 12

1.2 The Purpose of Natural Product Synthesis 13

1.3 Lamellarins and Related Pyrrolic Alkaloids Derived from Marine Organisms 14

1.3.1 The Lamellarin Family of Marine Alkaloids 14

1.3.1.1 Occurrence and Structural Elucidation 14

1.3.1.2 Proposed Biogenesis of the Lamellarins 18

1.3.1.3 Biological Activity 18

1.3.2 The Ningalins Family of Marine Alkaloids 21

1.3.2.1 Occurrence and Structural Elucidation 21

1.3.2.2 Biological Activity 22

1.3.3 Structural Comparison of the Lamellarins with Ningalin B 23

1.4 References 24

1 Introduction to Marine Alkaloids and Natural Product Synthesis

1.1 Natural Products from Marine Organisms

The marine environment is a source of many interesting and unique natural products. In contrast to the situation associated with terrestrially-derived natural products, bioactive molecules from marine sources are subject to a different set of criteria to meet the demands of the producing organisms, including those associated with communication and defence. On land, communication between species is often effected by pheromones. These are usually volatile compounds and necessarily, therefore, of relatively low molecular weight and structural complexity. As a consequence, they are generally easy to synthesise. Underwater, the most important aspect for communication is the water-solubility of the signalling molecules. This means that even very complex and large molecules can be involved as long as the water-solubility criterion is fulfilled.[1] Furthermore, since the marine environment is a relatively closed system that is often saline and subject to high pressures, but relatively constant temperatures, the chemical transformations involved are often distinctly different from those encountered on land.

Given these facts and the recent advances in SCUBA-diving, it is unsurprising to find the interest in the isolation of marine natural products has increased dramatically over the last few decades as evidenced by the rapidly increasing number of compounds of this type having been reported since the 1960's (Figure 1.1).[2]

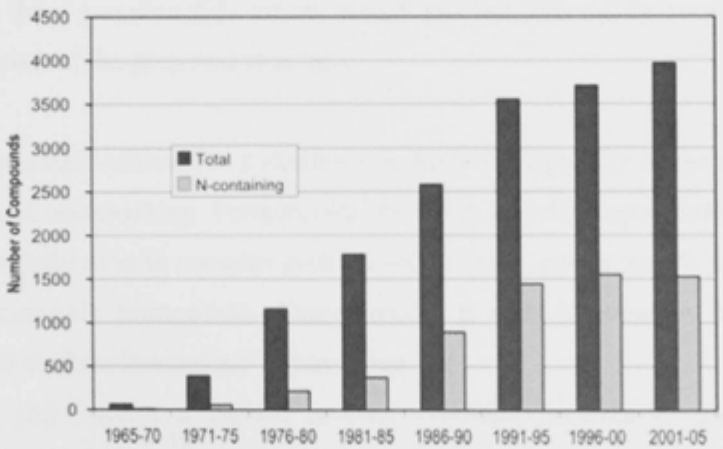


Figure 1.1: Number of Compounds Isolated from Marine Sources since the mid-1960's[2]

1.2 The Purpose of Natural Product Synthesis

There are several reasons for chemists to pursue the synthesis of natural products. Firstly, around half of the drugs now in clinical use are of natural product origin.[3] The reason for this high potency of naturally derived compounds, as compared to synthetic compounds, lies in evolutionary selection. Thus, through many years of evolution, nature has engineered molecules to interact in an optimal fashion with biological targets, especially protein binding sites. Among proteins, these biological targets are often very similar within different genetic sequences. Small molecules that have evolved for a certain purpose for one organism can have the same interactive effects with biological targets from different organisms resulting in distinct but, nevertheless, potent outcomes. However, the quantities of such compounds that can be obtained from 'Nature's drug cabinet'[3] are often extremely small and, therefore, insufficient to allow for a proper study of their potency and spectrum of biological activity. The obvious solution to this problem lies in 'imitating nature',[4] namely by synthesising such compounds in the laboratory.

Another significant motivation for undertaking the synthesis of a natural product is to confirm the proposed structure.[5] With the rapid development and refinement of spectroscopic techniques over the last few decades it has become easier to determine the structure of a natural product.[6] Nevertheless, certain aspects of structure elucidation remain controversial.[7] If the synthetic approach to a natural product is unambiguous and/or can be supported by a single-crystal X-ray analysis and the spectral data thus obtained are in full agreement with those recorded data for the natural product, this can be seen as representing definite verification of the proposed structure.

Lastly, natural product synthesis is a challenge to both the ingenuity of the chemist and the available synthetic methodology. Furthermore, the utility of a developed methodology can be evaluated by its application to complex systems and, thereby, giving access, in optimal cases, to hitherto inaccessible frameworks. Consequently, it adds information to the academic environment and furthers humankind's knowledge.
The challenge and interest a natural product synthesis presents to chemists will be demonstrated in the following Chapters.

1.3 Lamellarins and Related Pyrrolic Alkaloids Derived from Marine Organisms

1.3.1 The Lamellarin Family of Marine Alkaloids

1.3.1.1 Occurrence and Structural Elucidation

The lamellarins are one of the largest families of marine natural products that currently include some 54 compounds. These alkaloids have been isolated from a variety of marine organisms.[8]

Structurally speaking, the lamellarins can be divided into two subclasses with the simpler ones being comprised of a central pyrrole ring bearing a C2-carbomethoxy group, aryl groups at C3 and C4, as well as an N1-β-phenethyl moiety.[9] The aryl groups are always at least mono-oxygenated as can be seen in lamellarin O (**1**) (Figure 1.1), a representative member of this subclass. The second subclass is structurally more complex and the members of this one incorporate a pentacyclic framework as encountered, for example, in lamellarin A (**2**). The subclass of the so-called complex lamellarins can be further subdivided between those that incorporate a double bond between C5 and C6 and those that don't. So, lamellarin A (**2**) is member of the latter subclass while lamellarin D (**3**) is an example of the former. The presence of a double bond between these positions increases the planarity of the system and, therefore, enhances the ability of these unsaturated compounds to intercalate with DNA. This results in generally higher levels of cytotoxicity. The aryl substituent at C1 is, in general, orthogonally disposed to the main pentacyclic framework and the rotation around the linking bond is restricted, thus raising the possibility of atropisomerism.[10]

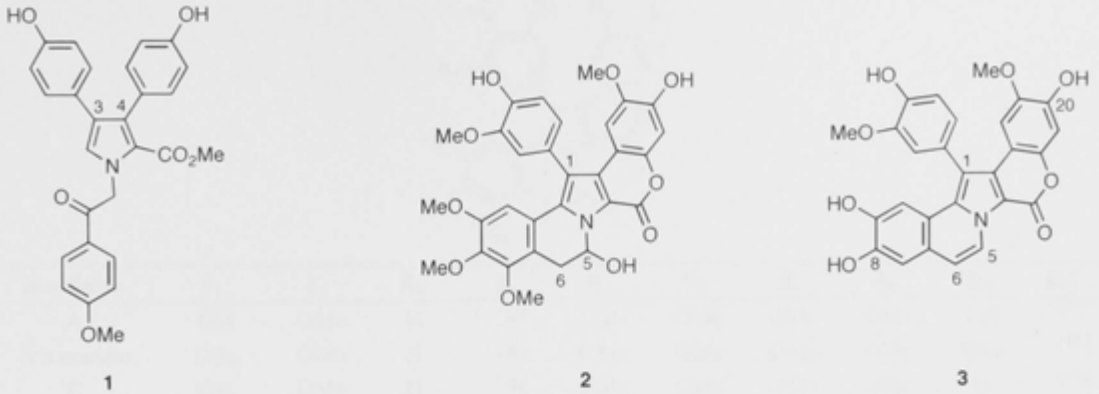


Figure 1.2: Structures of a Simple and Certain of the More Complex Lamellarins

Lamellarins A-D were isolated and identified in 1985 by Faulkner and coworkers from a prosobranch mollusc *Lamellaria* sp.[11] The structure of lamellarin A (**2**) was determined by single-crystal X-ray crystallography while the structures of lamellarins B-D were determined by spectroscopic methods. In 1988 Fenical's group isolated four additional lamellarins, E-H, from the marine tunicate *Didemnum chartaceum* collected in the Republic of Seychelles.[12] Since it is known that the family of *Lamellaria* sp. feeds on tunicates, it has been suggested that *Lamellaria* sp. acquire these alkaloids by dietary pathways.

A detailed discussion of the isolation, structural elucidation, biological properties and synthesis of the family of lamellarins is beyond the scope of this thesis. The reader is, therefore, referred to recent and comprehensive reviews that have been published on this topic.[8,10] The structures of all of the simple lamellarins, namely lamellarins O-R, isolated by Capon during the period 1994-1995,[13] are shown in Figure 1.3 and those of the complex lamellarins are presented in Tables 1.1 and 1.2.

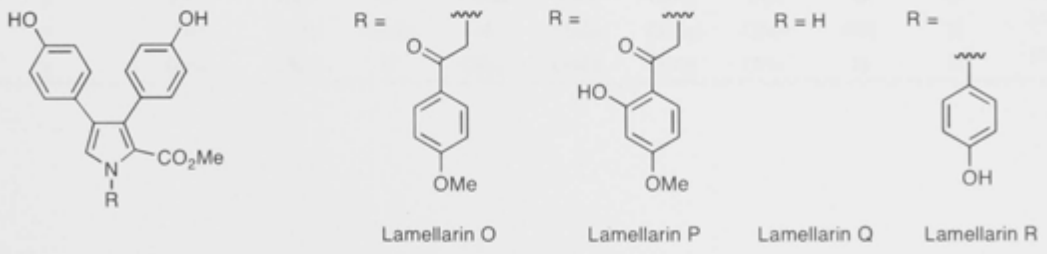
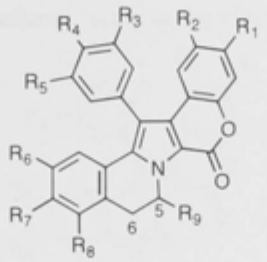


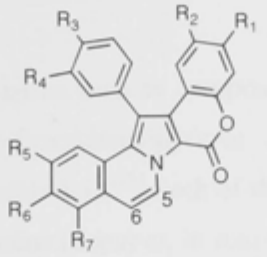
Figure 1.3: Structures of all Simple Lamellarins

Table 1.1: Structures of the Complex Lamellarins Incorporating a Single Bond between C5 and C6



lamellarin	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Ref.
A	OH	OMe	H	OH	OMe	OMe	OMe	OMe	OH	[11]
A triacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OMe	OAc	[11]
C	OH	OMe	H	OH	OMe	OMe	OMe	OMe	H	[11]
C diacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OMe	H	[14]
C 20-sulfate	OSO_3^-	OMe	H	OH	OMe	OMe	OMe	OMe	H	[15]
E	OH	OMe	H	OMe	OH	OMe	OMe	OH	H	[12]
F	OH	OMe	H	OMe	OMe	OMe	OMe	OH	H	[12]
G	OMe	OH	H	OMe	OH	OMe	OH	H	H	[12]
G 8-sulfate	OMe	OH	H	OMe	OH	OMe	OSO_3^-	H	H	[15]
I	OH	OMe	H	OMe	OMe	OMe	OMe	OMe	H	[16]
J	OH	OMe	H	OMe	OMe	OMe	OH	H	H	[16]
K	OH	OMe	H	OH	OMe	OMe	OMe	OH	H	[16]
K diacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OH	H	[14]
K triacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OAc	H	[14]
L	OH	OMe	H	OMe	OH	OMe	OH	H	H	[16]
L triacetate	OAc	OMe	H	OMe	OAc	OMe	OAc	H	H	[16]
L 20-sulfate	OSO_3^-	OMe	H	OMe	OH	OMe	OH	H	H	[15]
S	OH	OH	H	OH	OH	OMe	OH	H	H	[17]
T	OH	OMe	H	OMe	OH	OMe	OMe	OMe	H	[18]
T diacetate	OAc	OMe	H	OMe	OAc	OMe	OMe	OMe	H	[18]
T 20-sulfate	OSO_3Na	OMe	H	OMe	OH	OMe	OMe	OMe	H	[18]
U	OH	OMe	H	OMe	OH	OMe	OMe	H	H	[18]
U 20-sulfate	OSO_3Na	OMe	H	OMe	OH	OMe	OMe	H	H	[18]
V	OH	OMe	H	OMe	OH	OMe	OMe	OMe	OH	[18]
V 20-sulfate	OSO_3Na	OMe	H	OMe	OH	OMe	OMe	OMe	OH	[18]
Y 20-sulfate	OSO_3Na	OMe	H	OMe	OH	OH	OMe	H	H	[18]
Z	OMe	OH	H	OH	OH	OMe	OH	H	H	[15]
β	OH	OH	H	OMe	OH	OH	OH	H	H	[19]
γ	OH	OMe	OMe	H	OMe	OMe	OMe	OH	H	[14]
χ	OAc	OMe	H	OAc	OMe	OMe	OAc	H	H	[20]

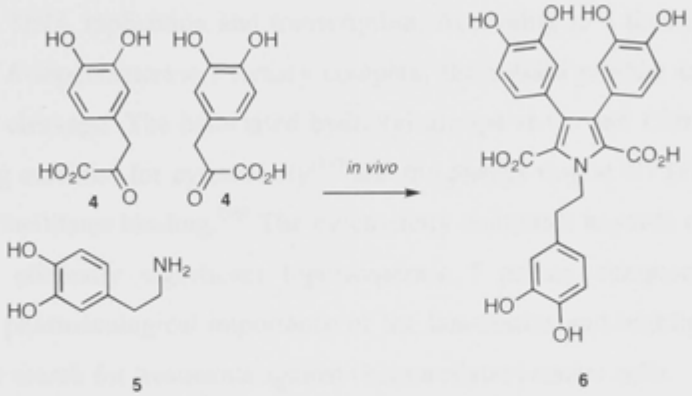
Table 1.2: Structures of the Complex Lamellarins Incorporating a Double Bond between C5 and C6



lamellarin	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Ref.
B	OH	OMe	OH	OMe	OMe	OMe	OMe	[11]
B diacetate	OAc	OMe	OAc	OMe	OMe	OMe	OMe	[11]
B 20-sulfate	OSO_3^-	OMe	OH	OMe	OMe	OMe	OMe	[15]
D	OH	OMe	OH	OMe	OH	OH	H	[11]
D triacetate	OAc	OMe	OAc	OMe	OMe	OAc	H	[16]
H	OH	OH	OH	OH	OMe	OH	H	[12]
M	OH	OMe	OH	OMe	OMe	OMe	OH	[16]
M triacetate	OAc	OMe	OAc	OMe	OMe	OMe	OAc	[16]
N	OH	OMe	OMe	OH	OMe	OH	H	[18]
N triacetate	OAc	OMe	OMe	OAc	OMe	OAc	H	[16]
W	OH	OMe	OMe	OH	OMe	OH	OMe	[18]
X	OH	OMe	OMe	OH	OMe	OMe	OH	[18]
X triacetate	OAc	OMe	OMe	OAc	OMe	OMe	OAc	[14]
α	OH	OMe	OMe	OH	OMe	OMe	H	[14]
α 20-sulfate	OSO_3Na	OMe	OMe	OH	OMe	OH	H	[21]
α 13,20-disulfate	OSO_3Na	OMe	OMe	OSO_3Na	OMe	OAc	H	[22]
ε	OH	OMe	OMe	OMe	OMe	OH	OH	[14]
ζ	OH	OMe	OMe	OMe	OMe	OH	OMe	[20]
η	OH	OMe	OMe	OMe	OMe	OMe	H	[20]
ϕ	OAc	OMe	OAc	OMe	OAc	OMe	OMe	[20]

1.3.1.2 Proposed Biogenesis of the Lamellarins

Biogenetically speaking, the lamellarins such as compound **6** are considered to be derived from two molecules of 3,4-dihydroxyphenylpyruvic acid **4** and a molecule of 3,4-dihydroxyphenylethylamine **5** (Scheme 1.1).[23] Each of these building blocks is presumed to come from 3,4-dihydroxyphenylalanine (dopa) or, in some cases, tyrosine.



Scheme 1.1: Proposed Biogenesis of Lamellarins

Thus, two molecules of **4** are believed to engage in an oxidative coupling reaction and so forming a 1,4-dicarbonyl compound that engages in a two-fold Schiff-base type condensation with β-phenethylamine **5** to afford fully substituted pyrrole **6**. This last compound is thought likely to be the progenitor to all lamellarins.

1.3.1.3 Biological Activity

As well as being structurally unique, the lamellarins also exhibit very significant and interesting biological properties.[8b,24] These include cytotoxic properties, antitumor activity, multidrug resistance (MDR) reversal properties, a capacity to inhibit HIV-1 integrase, antibiotic activity, human aldose reductase inhibition, inhibition of cell division, immunomodulatory activity, antioxidant activity and feeding deterrence. The commentary in the remaining parts of this Chapter is limited to a brief introduction to properties such as cytotoxicity and antitumor activity, MDR reversal and HIV-1 integrase inhibition.

Cytotoxicity and Antitumor Activity

Many of the lamellarins exhibit strong cytotoxicity against various cancer lines.[25] Among the more potent of them are lamellarins D, K and M which display activity in the mid-to-high nanomolar range (38-110 nM).[26] Lamellarin D (**3**) is the most potent of the lamellarins with a high cytotoxicity towards human prostate cancer cell lines (GI_{50} values against LNCaP and DU-145 are in the 10-20 nM range) and leukemia cell lines.[27] In 2003, lamellarin D was identified as a potent inhibitor of topoisomerase I,[28] an enzyme that relaxes supercoils generated during DNA replication and transcription. According to a theoretical model of a lamellarin D-DNA-topoisomerase I ternary complex, the natural product intercalates at the site of the DNA cleavage. The associated hydroxyl groups at C8 and C20 (Figure 1.1) are regarded as being essential for cytotoxicity[29] and the phenyl ring at C1 (Figure 1.1) serves as a 'hook' that facilitates binding.[30] The cytotoxicity continues towards cell lines that are resistant to the clinically significant topoisomerase I poison camptothecin, and thus emphasizing the pharmacological importance of the lamellarins and highlighting lamellarin D as a lead in the search for treatments against chemoresistant cancer cells.

High potency and good cytoselectivity are encountered in lamellarins H and α, which have been tested against a panel of eight human cancer cell lines. Interestingly, the selectivity patterns of these two compounds differed from one another.[22]

Multidrug Resistance (MDR) Reversal Activity

Disease-causing organisms have the ability to become resistant to a variety of drugs, which results, for example, in some anticancer drugs losing their potency against tumor cells. Certain lamellarins have the ability to reverse MDR at non-toxic concentrations by inhibiting P-glycoprotein (P-gp)-mediated efflux mechanisms.[26,28b,31] Prominent examples of compounds possessing such properties are lamellarin I and K, with lamellarin I being 9-16 times more effective as a MDR modulator than the approved anticancer agent verapamil.[26]

Inhibition of HIV-1 Integrase

The human immunodeficiency virus (HIV) encodes three enzymes, namely reverse transcriptase, protease and integrase that are critical to viral replication. While existing anti-

HIV-drugs target the first two of these enzymes, lamellarin α-20 sulfate has inhibitory effects, both *in vitro* and *in vivo*, on the last one.[21-22] Further studies indicate that lamellarin α-20 sulfate not only affects the core domain of integrase but the *N*- and *C*-terminal ones as well. As such this compound inhibits HIV integrase in a unique manner.[32] Among other lamellarins, lamellarin H was also found to be a potent inhibitor of the same integrase, although it acts with a lack of specificity.[22]

1.3.2 The Ningalins Family of Marine Alkaloids

1.3.2.1 Occurrence and Structural Elucidation

The members of the small family of alkaloids known as the ningalins have been isolated from an unidentified ascidian of the genus *Didemnum* collected, in 1997, in Western Australia near Ningaloo Reef.[33] The elucidation of the structures of these alkaloids was based on various forms of spectral analysis but especially 2D NMR techniques and then confirmed through unambiguous synthesis (see the following Chapter for details of this synthesis). The family consists of just four members, ningalins A-D, all of which (Figure 1.4) are highly polar and colored compounds containing a catechol moiety.

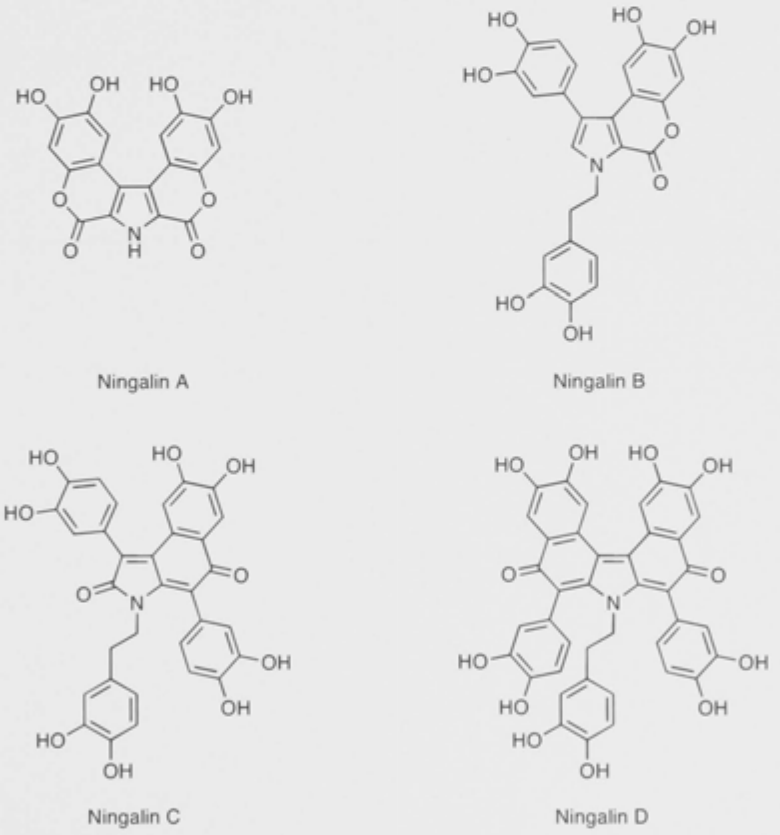


Figure 1.4: Structures of the Ningalins

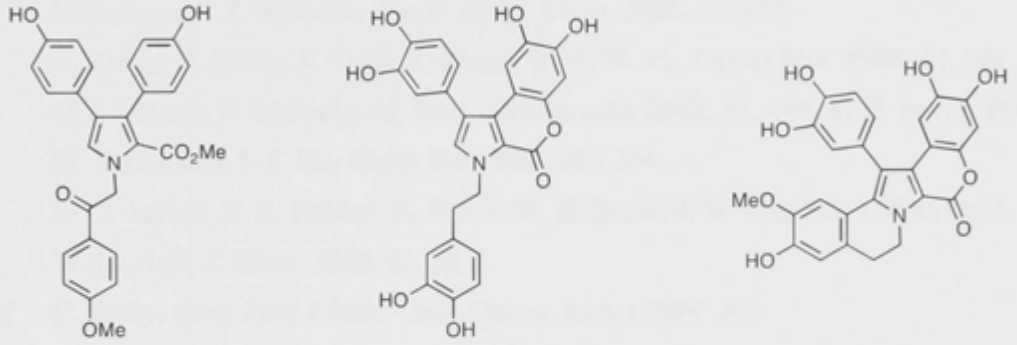
Although the ningalins are, in theory at least, capable of atropisomerism due to the highly congested nature of the constituent ring system none of those that have been isolated to date exhibited optical activity.

1.3.2.2 Biological Activity

The ningalins are less potent cytotoxic agents, in terms of their activity against cancer cell lines, than the lamellarins. Thus, only moderate cytotoxicity was displayed by ningalin D, permethyl ningalin D and ningalin D decaacetate against a murine leukaemia cell line.[34] However, ningalins B and D, as well as certain derivatives, are potent MDR reversal agents at non-cytotoxic concentrations.[35] In particular, ningalin B and its permethyl ether show a significant capacity to resensitize a human colon cancer line to vinblastine and doxorubicin, and have been demonstrated to be more effective than the standard MDR reversal agent verapamil. This puts them in the front line as candidates for the development of a new generation of MDR reversal agents. Additionally, the dimethylamide and amide derivatives of ningalin B and permethyl ningalin D were also found to have good MDR reversal capacities.[34]

1.3.3 Structural Comparison of the Lamellarins with Ningalin B

As noted earlier, the lamellarins can be subdivided into structurally simpler and more complex subclasses (see Section 1.3.1). The simpler ones are comprised of an unfused ring system as exemplified by lamellarin O (Figure 1.5) while the more complex ones, e.g. lamellarin S, possess a fully fused pentacyclic ring system. Accordingly, the structure of ningalin B with its tricyclic fused ring system can therefore be placed in between the simpler and the more complicated lamellarins and represents a 'transition' between them.



Lamellarin O | Ningalin B | Lamellarin S

Figure 1.5: Structural Comparison Between Ningalin B and the Simple and Complicated Lamellarins

Taking advantage of these structural similarities, the next chapter of this thesis is concerned with a synthesis of this 'halfway house'-type structure, as embodied in ningalin B, before exploiting the knowledge thus acquired in approaches to the synthesis of the more complicated lamellarins.

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2 *A Total Synthesis of the Marine Alkaloid Ningalin B from (S)-Proline*

2.1 Previous Syntheses of Ningalin B 28

2.2 Retrosynthetic Analysis of Ningalin B 34

2.3 Results and Discussion 35

2.3.1 Early Stages Associated with the Synthesis of Ningalin B 35

2.3.2 Synthesis of the Boronic Ester Coupling Partner **45** 38

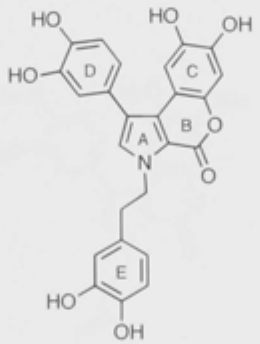
2.3.3 Completion of the Synthesis of Ningalin B 39

2.4 Summary and Conclusions 46

2.5 References 48

2 A Total Synthesis of the Marine Alkaloid Ningalin B from (*S*)-Proline

The marine alkaloid ningalin B (**7**) was isolated, together with three related pyrrole-containing natural products, by Fenical *et al.* from an ascidian belonging to the genus *Didemnum* which was collected from Ningaloo Reef in Western Australia.[1] The structure of ningalin B was first established by detailed NMR analyses and then confirmed through a total synthesis by Boger and co-workers (see below).[2] The biosynthesis of ningalin B is probably achieved through condensation reactions involving the amino acid 3,4-dihydroxyphenylalanine (DOPA). Similar processes are thought to lead to structurally related alkaloids such as the lamellarins, the lukianols, the polycitrins, and the stornioamides, all of which have attracted considerable attention because of their interesting biological properties (see Chapter 1).[3] Ningalin B has been implicated[1] in the pronounced metal-sesquestering capacities of the producing organism. However, it does not appear to display many other notable biological properties. Although ningalin B is not particularly cytotoxic,[2] its permethyl ether and various amide derivatives do show a significant capacity to reverse multi-drug resistance (MDR) by, for example, resensitising a resistant human colon cancer cell line HCT116/VM46 to vinblastine and doxorubicin.[2,4] As such these ningalin B derivatives behave in a similar fashion to certain of the lamellarins and their derivatives.[3]

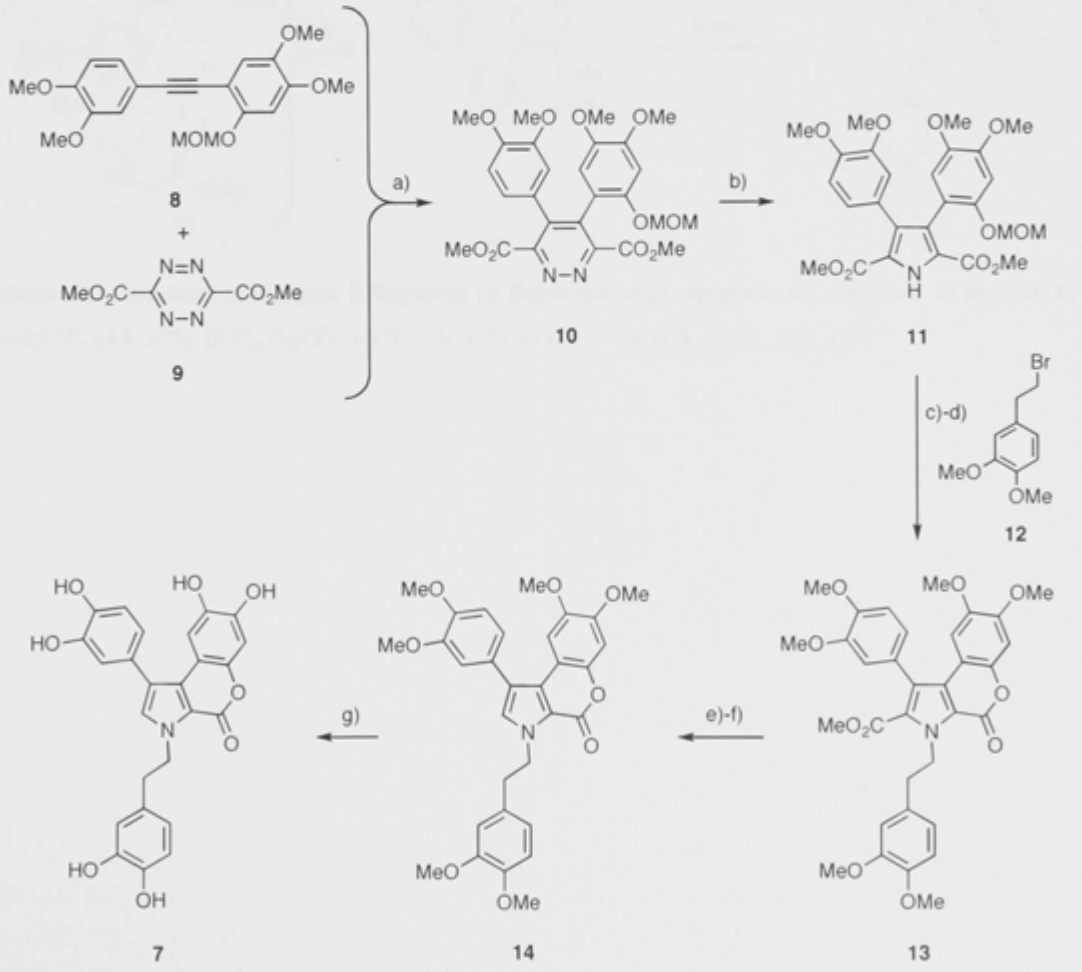


7

Figure 2.1: Structure of Ningalin B

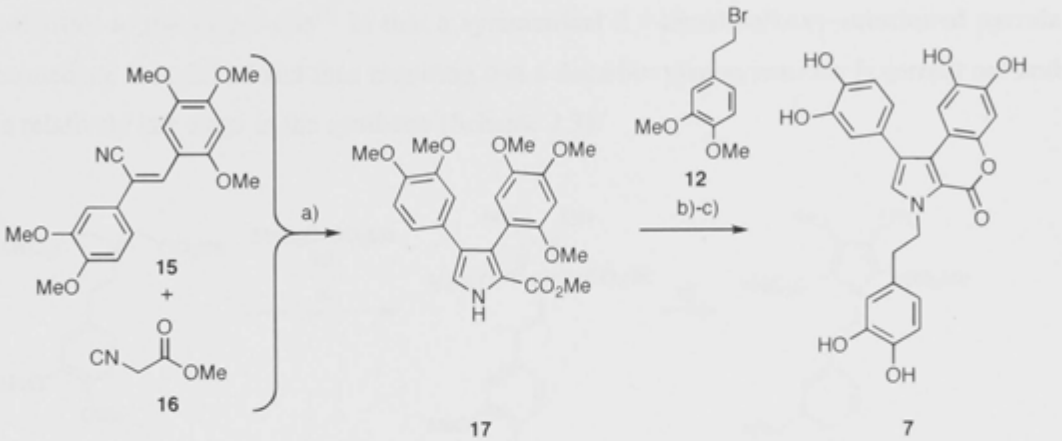
2.1 Previous Syntheses of Ningalin B

Ningalin B has been the subject of several synthetic studies, the first of which was reported by Boger *et al.*[2] in 2000 (Scheme 2.1). This group employed a heterocyclic azadiene Diels-Alder cycloaddition reaction between diphenylacetylene **8** and tetrazine **9** to give diazine **10**. A zinc-metal induced ring-contraction protocol was then applied to construct the tetrasubstituted pyrrole **11**. After modification of the pyrrole, through *N*-alkylation, lactonisation and decarboxylation [steps c)-f)], the permethyl ether of ningalin B (**14**) was obtained. Exhaustive demethylation then gave, in 98% yield, ningalin B itself.



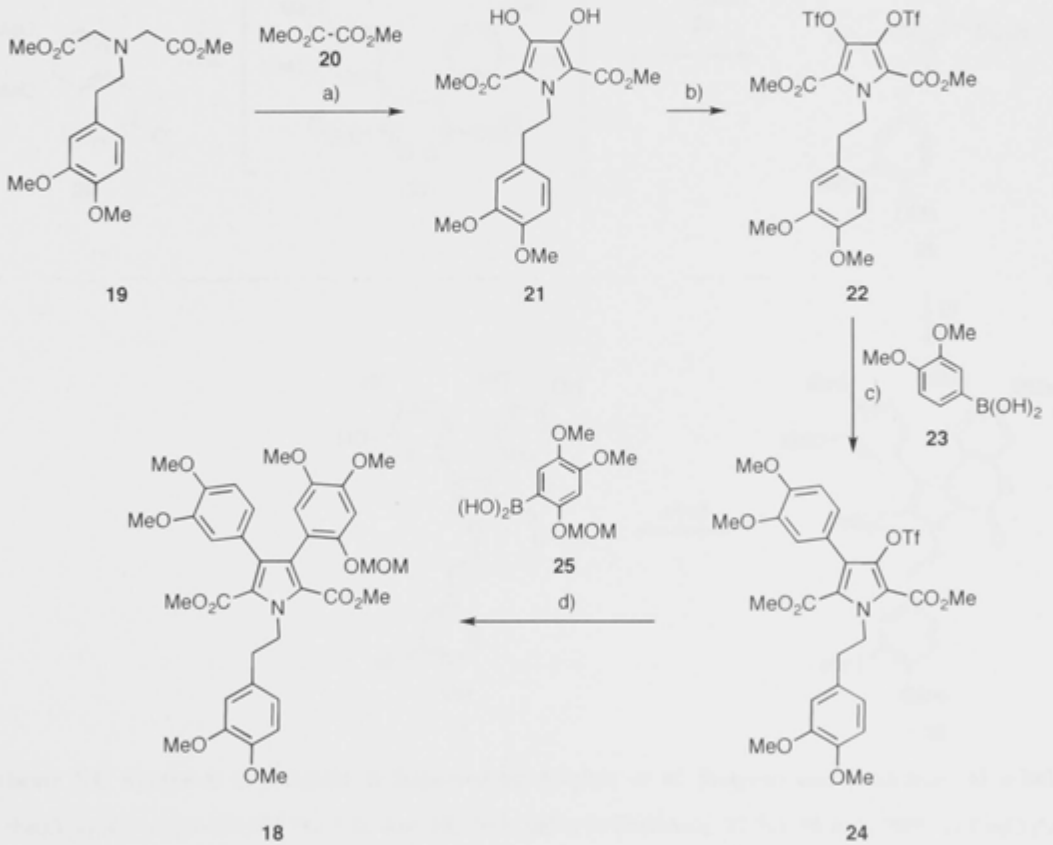
Scheme 2.1: Synthesis of Ningalin B Reported by Boger *et al.* *Reagents and conditions:* a) 140 °C, 48 h, 92%; b) Zn, AcOH, 25 °C, 15 h, 62%; c) **12** (5.0 eq.), K_2CO_3, 70 °C, 3 h, 94%; d) HCl-EtOAc, 25 °C, 2 h, 95%; e) LiI, 110 °C, 60 h, 80%; f) Cu_2O, 220 °C, 5 min, 70%; g) BBr_3, −78 °C→25 °C, 24 h, 98%.

The Bullington synthesis of ningalin B[5] was reported in 2002 and is quite distinct in that a symmetrical intermediate was not involved and no decarboxylation step was required (Scheme 2.2). The particularly concise synthesis starts with a base-promoted [2+3] 'cycloaddition' reaction between the α-cyanostilbene **15** and methyl isocyanoacetate (**16**) to give a trisubstituted pyrrole **17** that is readily *N*-alkylated, demethylated, and lactonised to give the target compound.



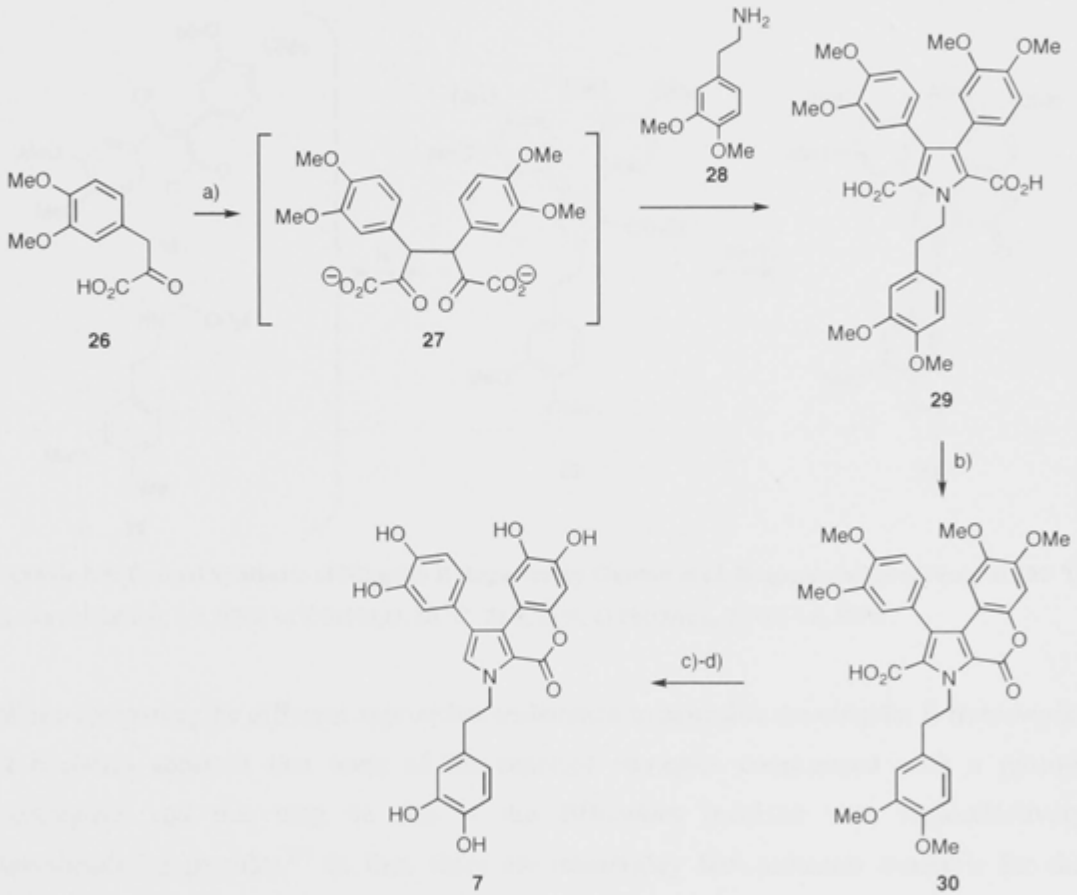
Scheme 2.2: Synthesis of Ningalin B Reported by Bullington *et al.* *Reagents and conditions:* a) *tert*-BuOK, 0→25 °C, 18 h, 57%; b) **12**, Cs_2CO_3, 60 °C, 3 h, 92%; c) BBr_3, −78→25 °C, *ca.* 16 h, 98%.

Iwao's formal synthesis of target **18**, reported in 2003 (Scheme 2.3),[6] used a Hinsberg-type condensation of the iminodiacetate **19** with dimethyl oxalate **20** to produce the symmetric 2,5-dicarboalkoxy-substituted pyrrole **21**. This pyrrole was converted into the *bis*-triflate **22** and this was, in turn, subjected to a Suzuki cross-coupling reaction with 3,4-dimethoxyphenyl boronic acid **23**, which gave the desymmetrised pyrrole **24**. A second cross-coupling reaction followed, thus producing the MOM-protected pyrrole **18** common to the route used by Boger *et al.* as shown in Scheme 2.1. Iwao's approach, therefore, has some similarities to the Boger one[2] in that a symmetrical 2,5-dicarboalkoxy-substituted pyrrole intermediate is involved and thus requiring that a decarboxylation reaction is carried out and at a relatively late stage in the synthesis (Scheme 2.3).



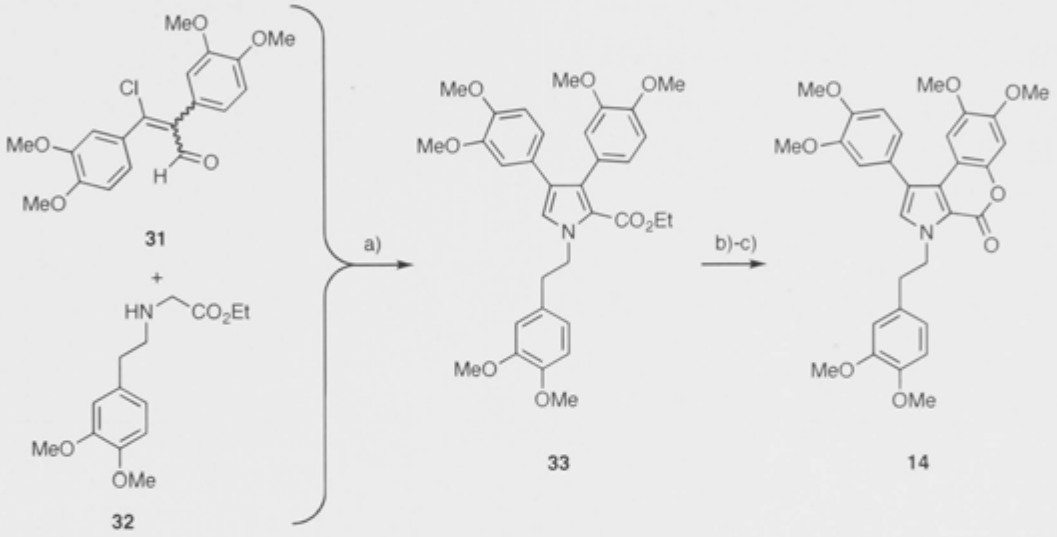
Scheme 2.3: Formal Synthesis of Ningalin B Reported by Iwao *et al.* *Reagents and conditions:* a) **20**, MeONa, 65 °C, 18 h, 49%; b) $(CF_3SO_2)_2O$, 0 °C, 2 h, 87%; c) **23** (1.0 eq.), $Pd(PPh_3)_4$, aq. Na_2CO_3, 66 °C, 4 h, 78%; d) **25** (2.0 eq.), $Pd(PPh_3)_4$, aq. Na_2CO_3, 66 °C, 20 h, 58%.

The Steglich synthesis of ningalin B (Scheme 2.4), which was reported in 2006,[7] is modelled on the proposed biogenesis of the natural product. The early stages involved the oxidative coupling of two molecules of aryl pyruvic acid **26** to form a 1,4-diketone **27** which was reacted *in situ* with 2-arylethylamine **28** to deliver the symmetrical penta-substituted pyrrole **29**. Lactonisation was achieved through exposure of compound **29** to lead tetra-acetate and through further modifications of product **30**, the synthesis of ningalin B was completed after late-stage decarboxylation and deprotection reactions.



Scheme 2.4: Synthesis of Ningalin B Reported by Steglich *et al.* *Reagents and conditions:* a) *n*-BuLi (2.0 eq.), I_2 (0.5 eq.), −78→25 °C, 1 h, then **28**, 16 h, 66%; b) $Pb(OAc)_4$, 77 °C, 45 min, 96%; c) $Cu_2Cr_2O_5$, 180 °C, 35 min, 93%; d) BBr_3, −78→25 °C, 16 h, 89%.

Gupton's synthesis of ningalin B permethyl ether, reported in 2009, involved the use of a versatile method for forming pyrroles from vinylogous iminium salts. The required β-chloroenal **31**, synthesised in three steps from commercially available starting material, was reacted with the *N*-substituted glycine derivative **32** to form the 2,3,4-substituted pyrrole **33** (Scheme 2.5).[8] As with the Bullington approach, symmetrical intermediates were not involved and, after saponification, the final step of the formal total synthesis utilised a 'Steglich-type' lead tetraacetate-mediated lactonisation reaction.[7]



Scheme 2.5: Formal Synthesis of Ningalin B Reported by Gupton *et al.* *Reagents and conditions:* a) 150 °C (μ-wave heating), 3 h, 97%; b) KOH/H_2O, 80 °C, 24 h, 68%; c) $Pb(OAc)_4$, 77 °C, 5 h, 52%.

When comparing the different approaches undertaken to assemble the ningalin B framework, it becomes apparent that none of the reported strategies commenced with a pyrrole centrepiece and this may be due to the difficulties involved with regioselectively functionalising pyrroles.[9] In fact, there are remarkably few protocols available for the regioselective halogenation of pyrrole esters beyond the selective preparation of 4-halopyrrole carboxylates reported by Bélanger *et al.*[10] and the related methodology reported by Smith *et al.*,[9b] in which the 4-position is blocked and thus allowing for halogenation of the remaining positions.

The Banwell group's continuing interest in the chemistry of pyrroles and their application to natural product synthesis has resulted in a new approach to ningalin B being established by the author. This is discussed in detail in the remainder of this Chapter. It represents the first

involving a pyrrole centrepiece and the necessary assembly of the remaining functionalities around it.

2.2 Retrosynthetic Analysis of Ningalin B

The approach to ningalin B presented herein relies on the elaboration of a pre-functionalised pyrrole core. As shown in Figure 2.2, this strategy focuses on the use of sequential halogenation/cross-coupling reactions to produce permethylated ningalin B (**14**), a previously reported and late-stage precursor to the natural product itself (see above). The proposed precursor to permethyl ningalin B (**14**) was to be the product of regioselective bromination of tricycle **34** at the 4-position (Figure 2.2). Tricycle **34** itself could be assembled through a cross-coupling reaction and spontaneous lactonisation reaction from precursor **35**. The last compound could be synthesised through *N*-alkylation of the pyrrole **36** which has been previously synthesised from (*S*)-proline (**37**) by members of the Banwell group.[11]

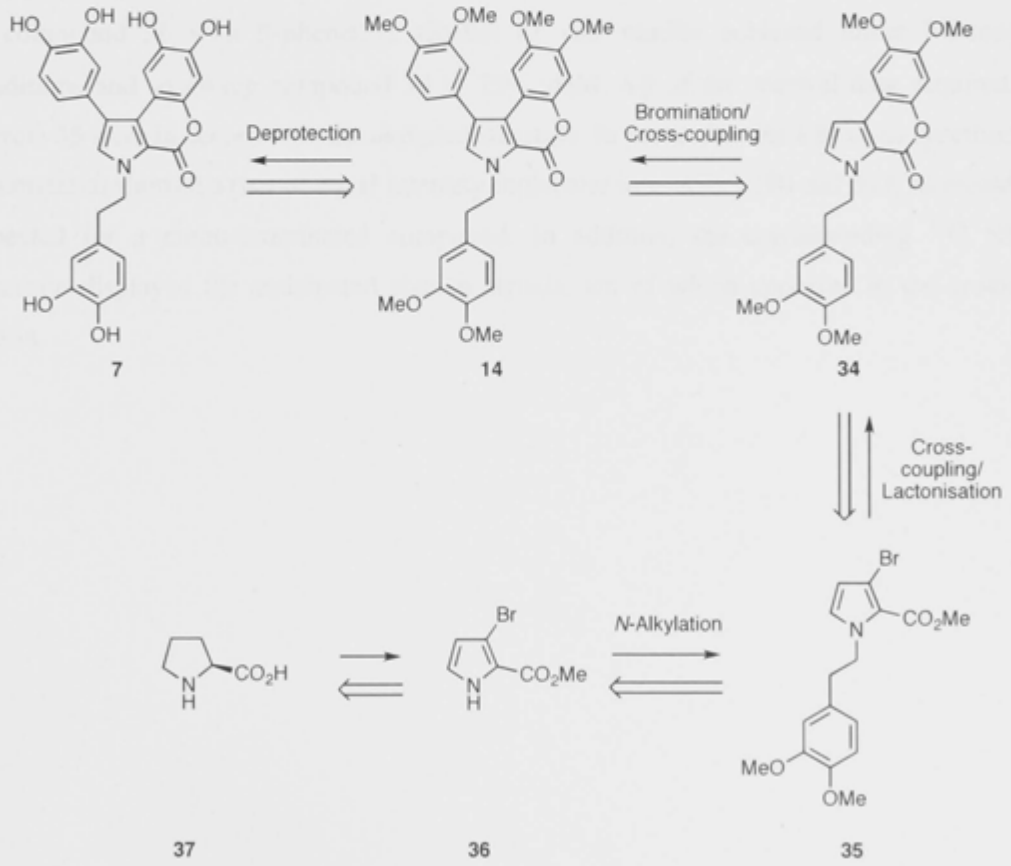
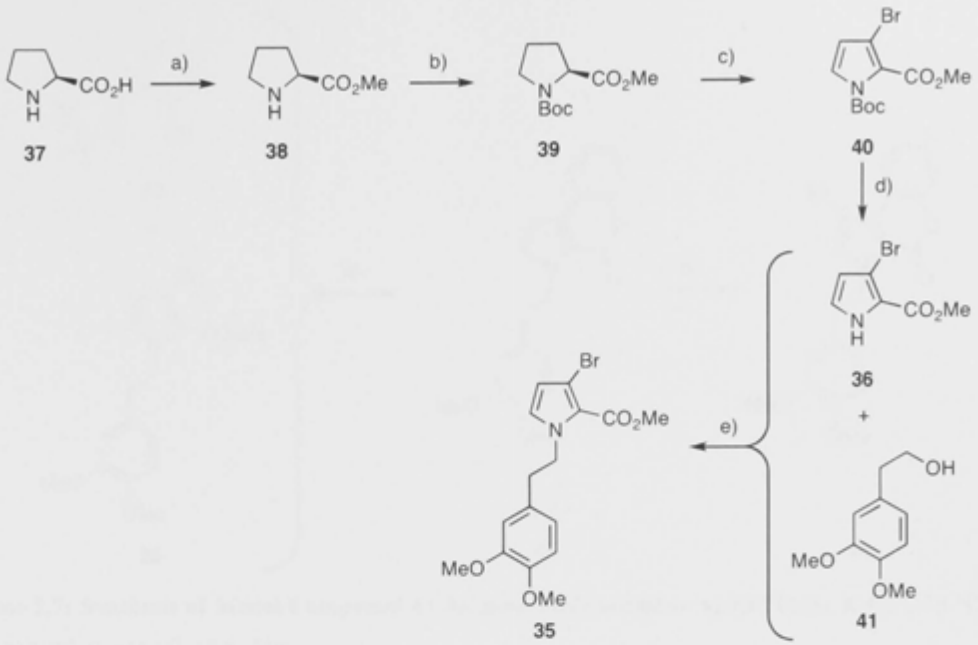


Figure 2.2: Retrosynthetic Analysis of Ningalin B Associated with Present Work

2.3 Results and Discussion

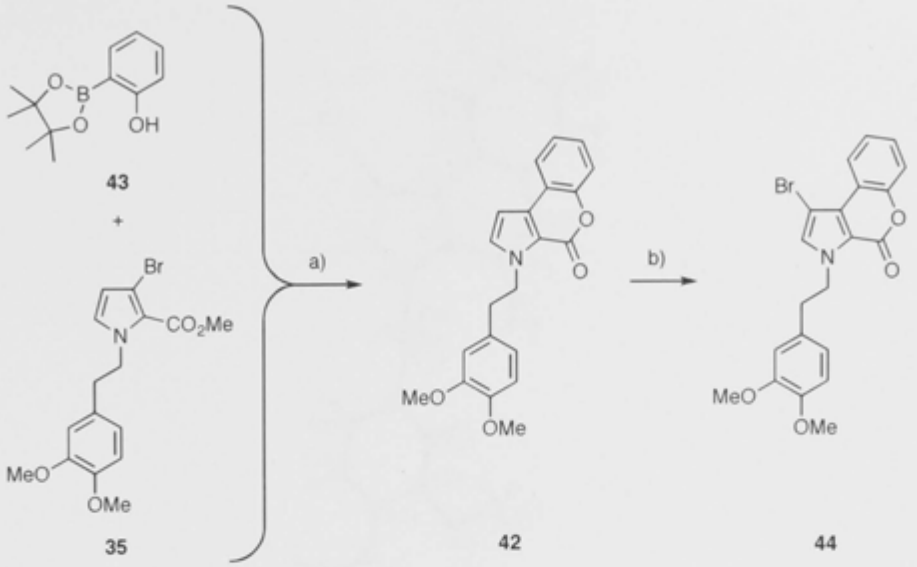
2.3.1 Early Stages Associated with the Synthesis of Ningalin B

The early stages of the synthesis of ningalin B are shown in Scheme 2.6 and involve the conversion of (*S*)-proline (**37**) into 3-bromo-2-carbomethoxypyrrole (**36**) using a novel oxidative bromination protocol first described by Easton *et al.*[12] and recently refined by Banwell and coworkers.[11] The substrate for this key step was prepared by converting acid **37** into the corresponding and well-known methyl ester **38** by using methanol and thionyl chloride. Boc-protection of the secondary amine within **38** afforded carbamate **39**, that was then brominated, in 72% yield, with *N*-bromosuccinimide in refluxing carbon tetrachloride.[11] Treatment of product **40** with zinc bromide readily cleaved the Boc protecting group to give the pivotal pyrrole **36** in 89% yield and its structure was confirmed through a single-crystal X-ray analysis carried out during earlier studies.[11] The *N*-alkylation of compound **36** with β-phenethyl alcohol **41** was readily achieved under Mitsunobu conditions and so giving compound **35** in 75% yield. All of the spectral data acquired on pyrrole **35** were in accord with the assigned structure. In particular, the ESI mass spectrum of this material showed a pair of equal intensity molecular ions at *m/z* 390 and 392, as would be expected for a mono-brominated compound. In addition, the corresponding ^{13}C NMR spectrum displayed the anticipated sixteen signals, ten of which appeared in the aromatic region.



Scheme 2.6: Synthesis of Cross-coupling Precursor 35 *Reagents and conditions:* a) $SOCl_2$, MeOH, 0→18 °C, 16 h, 88%; b) Boc_2O, Hünig's base, 18 °C, 15 h, 100%; c) NBS, 85 °C, 1 h, 72%; d) $ZnBr_2$, 18 °C, 5 h, 89%; e) DIAD, PPh_3, 18 °C, 15 h, 75%.

At this point, a model study was conducted so as to explore the conversion of pyrrole **35** into a compound (**42**) that, conveniently, represented the lactone core of ningalin B (Scheme 2.7). Thus, pyrrole **35** was subjected to a Suzuki-Miyaura cross-coupling reaction with the commercially available aryl boronic ester **43**. In accord expectation, a spontaneous lactonisation did indeed take place and so the product of the cross-coupling process was compound **42**. This was obtained in 79% yield.



Scheme 2.7: Synthesis of Model Compound 44 *Reagents and conditions:* a) $Pd(PPh_3)_4$, K_2CO_3, 70 °C, 1 h, 79%; b) NBS, 0→18 °C, 18 h, 74%.

The reaction of lactone **42** with *ca.* two molar equivalents of NBS in DMF at 0 °C provided a single mono-brominated derivative in 74% yield. While it was expected, on electronic grounds, to be the required bromide, namely compound **44**, the identity of the product could not be unambiguously assigned using NMR spectroscopic methods. Accordingly, the compound was subjected to a single-crystal X-ray analysis. The derived ORTEP plot is shown in Figure 2.3 and this clearly reveals that the desired bromopyrrole **44** had been obtained. The acquisition of compound **44**, which incorporates a bromine in the appropriate position for a second Suzuki cross-coupling reaction, allows for installation of the isolated aryl unit of ningalin B. This was a pleasing outcome and its adaptation to the synthesis of the natural product itself was thus pursued. The outcomes of these studies are detailed in the following sections.

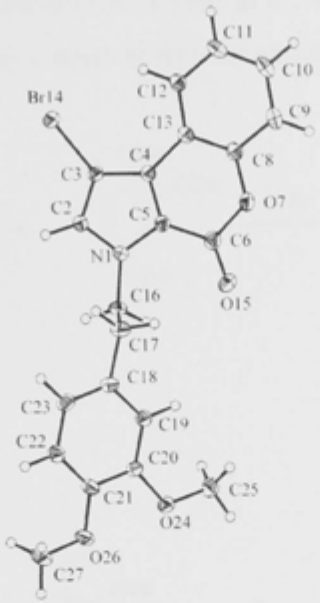
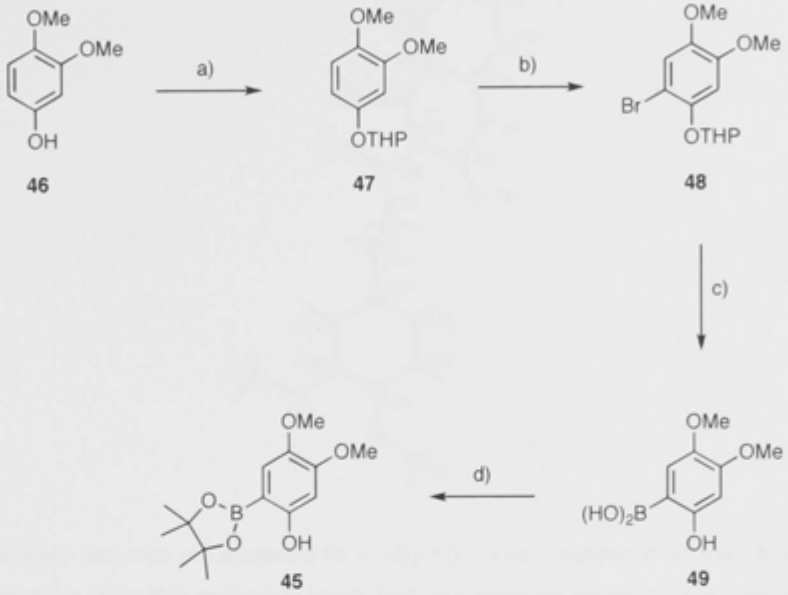


Figure 2.3: Molecular Structure of Compound **44** ($C_{21}H_{14}BrNO_4$) with Labelling of Selected Atoms (anisotropic displacement ellipsoids show 30% probability levels; hydrogen atoms are drawn as circles with small radii).

2.3.2 Synthesis of the Boronic Ester Coupling Partner 45

The completion of the synthesis of ningalin B from compound **35** required the synthesis of the relevant dimethoxylated analogue of aryl boronate **43** which was expected to participate in a Suzuki-Miyaura cross-coupling reaction with compound **35**. Handy *et al.* have described[9a] the preparation of such a species, namely 2-hydroxy-4,5-dimethoxyphenyl boronic acid and therefore their method was used to prepare this compound. However, this boronic acid was found to be unstable and, therefore, difficult to purify. Accordingly, the synthesis of the corresponding pinacolato derivative (**45**) was pursued using a modification of Handy's protocols.[9a] The reaction sequence used is shown in Scheme 2.8 and starts with the conversion, under standard conditions, of commercially available 3,4-dimethoxyphenol (**46**) into the corresponding THP ether **47**.[9a] Bromination of this last compound using NBS in DMF proceeded smoothly to afford the required bromide **48**[9a] in 83% yield over the two steps. Metallation of halide **48** with *n*-BuLi and subjection of the resulting aryl lithium to tri-isopropylborate followed by acidic work up then afforded Handy's boronic acid **49**. After reaction of acid **49** with pinacol, the ester **45** was obtained as a white crystalline solid in 69% overall yield from precursor **48**. The EI mass spectrum of compound **45** showed a molecular ion at *m/z* 280 while the ^{1}H NMR spectrum showed two one-proton singlets in the 'aromatic'

region (δ 6.95 and 6.40), two three-proton singlets at δ 3.81 and 3.80 and a twelve-proton singlet at δ 1.21, all of which were consistent with the structure of product **45**.



Scheme 2.8: Synthesis of Boronic Ester 45 *Reagents and conditions:* a) DHP, PPTS, 18 °C, 2 h, 100%; b) NBS, Na_2CO_3, 0→18 °C, 3 h, 83%; c) $B(OiPr)_3$, *n*-BuLi, −78→18 °C, 12 h, then HCl; d) pinacol, 18 °C, 24 h, 69% (over three steps).

2.3.3 Completion of the Synthesis of Ningalin B

With the relevant coupling partners in hand, namely compounds **35** and **45**, these were then subjected to a Suzuki-Miyaura cross-coupling process (Scheme 2.9) and this provided the anticipated lactone **34**, albeit in just 43% yield. The NMR spectral data obtained on this product were completely consistent with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 2.4.

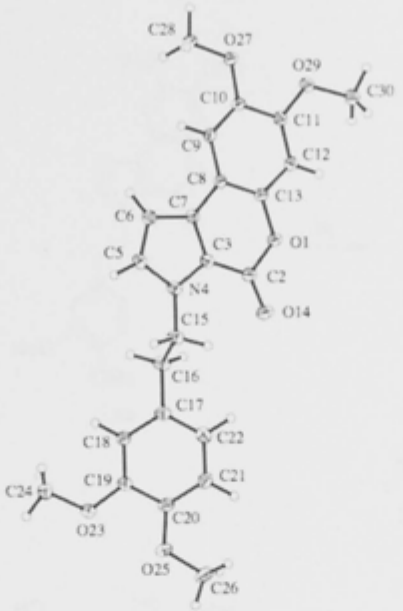
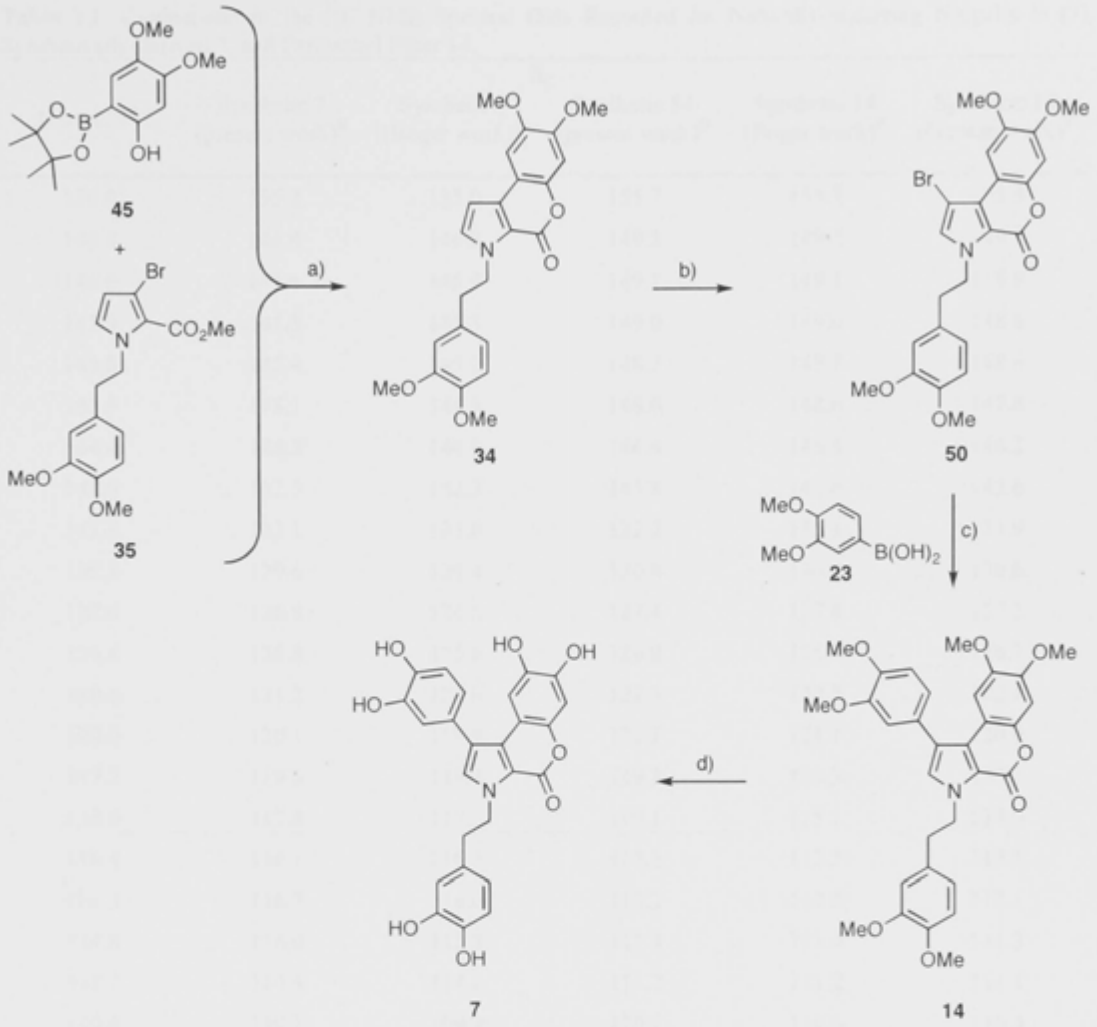


Figure 2.4: Molecular Structure of Compound **34** ($C_{23}H_{23}NO_6$) with Labelling of Selected Atoms (anisotropic displacement ellipsoids show 30% probability levels; hydrogen atoms are drawn as circles with small radii).

Various modifications to the procedure used for the conversion **35** → **34** failed to provide the latter compound in higher yield. Nevertheless, sufficient quantities of it could be accumulated through the original procedure so as to allow for completion of the synthesis of ningalin B. To such ends, this material was brominated with NBS in DMF and the ensuing bromide **50** (97%) was then cross-coupled with the commercially available arylboronic acid **23** to give the previously reported[2] ningalin B permethyl ether **14** in 69% yield. Following a protocol established by Boger *et al.*,[2] treatment of this last compound with boron tribromide in hexane at –78 °C with subsequent warming to 18 °C effected exhaustive demethylation and thus gave ningalin B (**7**) in 94% yield.



Scheme 2.9: Synthesis of Ningalin B *Reagents and conditions:* a) $Pd(PPh_3)_4$, Cs_2CO_3, 80 °C, 4 h, 43%; b) NBS, 0→18 °C, 4 h, 97%; c) **23**, $Pd(PPh_3)_4$, K_2CO_3, 80 °C, 1 h, 69%; d) BBr_3, −78→18 °C, 16 h, 96%.

The ^{13}C and ^{1}H NMR spectral data derived from compounds **7** and **14** (Tables 2.1 and 2.2, respectively) compare very favourably with those reported previously. The slight variations between the carbon chemical shifts recorded for naturally derived ningalin B and those arising from the synthetic material can be attributed to the differing solvent systems used to record the cited data.

Table 2.1: Comparison of the ^{13}C NMR Spectral Data Recorded for Naturally-occurring Ningalin B (**7**), Synthetically-derived **7**, and Permethyl Ether **14**.

			δ_C		
Natural **7**[A]	Synthetic **7** (present work)[B]	Synthetic **7** (Boger work)[C]	Synthetic **14** (present work)[D]	Synthetic **14** (Boger work)[E]	Synthetic **14** (Gupton work)[F]
156.0	155.2	155.0	155.7	155.7	155.5
146.8	146.4	146.2	149.2	149.2	149.1
146.0	145.6	145.4	149.1	149.1	148.9
145.9	145.5	145.3	149.0	149.0	148.8
145.8	145.4	145.2	148.7	148.7	148.6
145.5	145.1	144.9	148.0	148.0	147.8
144.4	144.2	144.0	146.4	146.4	146.2
142.9	142.5	142.3	145.8	145.8	145.6
133.5	133.1	133.0	132.2	132.1	131.9
130.2	129.6	129.4	130.8	130.7	130.6
127.6	126.8	126.6	127.4	127.4	127.2
126.4	125.8	125.6	126.9	126.9	126.7
120.6	121.2	121.0	122.3	122.3	122.1
120.0	120.1	119.9	121.1	121.1	120.0
117.7	119.6	119.4	119.3	119.3	119.1
116.9	117.4	117.2	115.1	115.1	114.9
116.4	116.7	116.4	113.2	113.2	113.1
116 .1	116.2	116.0	112.2	112.3	112.1
114.8	116.0	115.8	111.4	111.4	111.3
112.7	114.4	114.2	111.2	111.2	111.1
110.6	110.1	109.9	110.7	110.6	110.4
109.3	109.0	108.8	104.9	104.9	104.8
104.0	103.9	103.7	100.8	100.8	100.6
50.9	50.4	50.2	56.4	56.3	56.1
37.9	37.6	37.4	56.3	56.2	56.0
			56.11 (1C) 56.1(0) (2 C)	56.1 (3 C)	55.9
			56.0	56.0	55.8
			51.3	51.3	51.0
			38.0	38.0	37.8

[A] Data from ref. [1] and recorded in 5:1 v/v $[D_6]DMSO/CD_3OD$ at 125 MHz.

[B] Data arising from work reported herein and recorded in 79% $[D_6]DMSO$/21% CD_3OD at 75 MHz.

[C] Data from ref. [2] and recorded in 83% $[D_6]DMSO$/17% CD_3OD at 100 MHz.

[D] Data arising from work reported herein and recorded in $CDCl_3$ at 75 MHz.

[E] Data from ref. [2] and recorded in $CDCl_3$ at 100 MHz.

[F] Data from ref. [8] and recorded in $CDCl_3$ at 125 MHz.

Table 2.2: Comparison of the ^{1}H NMR Spectral Data Recorded for Naturally-occurring Ningalin B (**7**), Synthetically-derived **7**, and Permethyl Ether **14**.

			δ_H		
Natural **7**[A]	Synthetic **7** (present work)[B]	Synthetic **7** (Boger work)[C]	Synthetic **14** (present work)[D]	Synthetic **14** (Boger work)[E]	Synthetic **14** (Gupton work)[F]
7.13 (s, 1H)	7.15 (s, 1H)	7.17 (s, 1H)	7.09 (s, 1H)	7.09 (s, 1H)	7.09 (s, 1H)
7.06 (s, 1H)	7.05 (s, 1H)	7.07 (s, 1H)	6.95-6.92 (m, 3H)	6.95-6.92 (m, 3H)	6.96-6.92 (m, 3H)
6.86 (d, *J* 8 Hz, 1H)	6.79 (d, *J* 8.1 Hz, 1H)	6.80 (d, *J* 8.2 Hz, 1H)	6.88 (bs, 1H)	6.88 (d, *J* 1.2 Hz, 1H)	6.88 (d, *J* 1.4 Hz, 1H)
6.84 (d, *J* 1.5 Hz, 1H)	6.76 (d, *J* 2.1 Hz, 1H)	6.77 (d, *J* 2.0 Hz, 1H)	6.79 (d, *J* 8.2 Hz, 1H)	6.79 (d, *J* 8.2 Hz, 1H)	6.79 (d, *J* 8 Hz, 1H)
6.80 (s, 1H)	6.74 (s, 1H)	6.75 (s, 1H)	6.74 (s, 1H)	6.74 (s, 1H)	6.74 (s, 1H)
6.70 (dd, *J* 8 and 1.5 Hz, 1H)	6.63 (dd, *J* 8.1 and 1.5 Hz, 1H)	6.63 (m, 2H)	6.71 (dd, *J* 8.2 and 1.8 Hz, 1H)	6.71 (dd, *J* 7.9 and 1.8 Hz, 1H)	6.70 (dd, *J* 8 and 2 Hz, 1H)
6.67 (d, *J* 8 Hz, 1H)	6.60 (d, *J* 8.1 Hz, 1H)		6.58 (d, *J* 1.8 Hz, 1H)	6.58 (d, *J* 1.5 Hz, 1H)	6.58 (d, *J* 1.5 Hz, 1H)
6.60 (d, *J* 1.5 Hz, 1H)	6.57 (d, *J* 2.1 Hz, 1H)	6.59 (d, *J* 1.8 Hz, 1H)	4.65 (t, *J* 7.0 Hz, 2H)	4.65 (t, *J* 7.0 Hz, 2H)	4.65 (t, *J* 7 Hz, 2H)
6.47 (dd, *J* 8 and 1.5 Hz, 1H)	6.41 (dd, *J* 8.1 and 1.5 Hz, 1H)	6.43 (dd, *J* 7.9 and 2.1 Hz, 1H)	3.93 (s, 3H)	3.93 (s, 3H)	3.92 (s, 3H)
4.55 (t, *J* 7.3 Hz, 2H)	4.47 (t, *J* 7.2 Hz, 2H)	4.54 (t, *J* 7.0 Hz, 2H)	3.91 (s, 3H)	3.91 (s, 3H)	3.90 (s, 3H)
2.94 (t, *J* 7.3 Hz, 2H)	2.85 (t, *J* 7.2 Hz, 2H)	2.92 (t, *J* 7.4 Hz, 2H)	3.87 (s, 3H)	3.87 (s, 3H)	3.87 (s, 3H)
			3.85 (s, 3H)	3.85 (s, 3H)	3.84 (s, 3H)
			3.77 (s, 3H)	3.77 (s, 3H)	3.76 (s, 3H)
			3.57 (s, 3H)	3.57 (s, 3H)	3.56 (s, 3H)
			3.11 (t, *J* 7.0 Hz, 2H)	3.11 (t, *J* 7.0 Hz, 2H)	3.07 (t, *J* 7 Hz, 2H)

[A] Data from ref. [1] and recorded in 5:1 v/v $[D_6]DMSO/CD_3OD$ at 500 MHz.

[B] Data arising from work reported herein and recorded in 79% $[D_6]DMSO$/21% CD_3OD at 300 MHz.

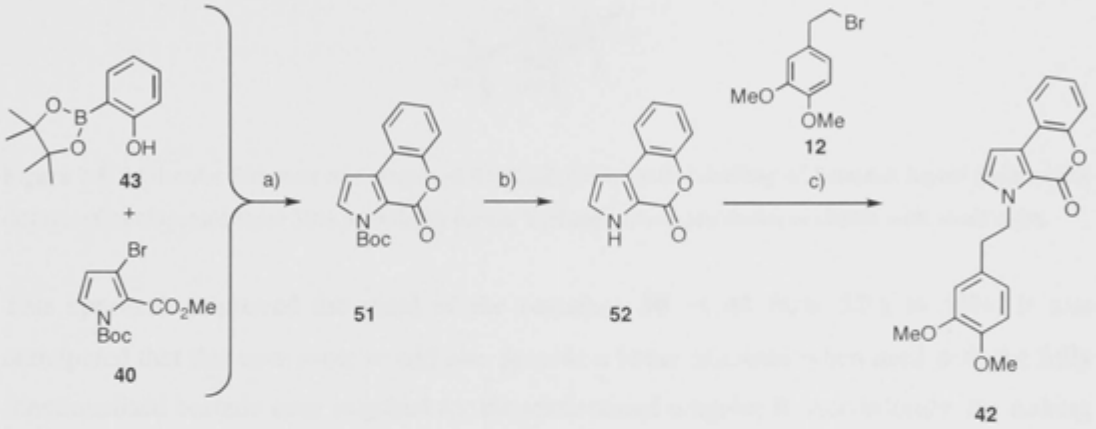
[C] Data from ref. [2] and recorded in 83% $[D_6]DMSO$/17% CD_3OD at 400 MHz.

[D] Data arising from work reported herein and recorded in $CDCl_3$ at 300 MHz.

[E] Data from ref. [2] and recorded in $CDCl_3$ at 400 MHz.

[F] Data from ref. [8] and recorded in $CDCl_3$ at 500 MHz.

In an effort to establish an improved synthesis of ningalin B, alternate points in the abovementioned reaction sequence at which the pivotal Suzuki-Miyaura cross-coupling reaction involving compound **45** could be carried out were investigated. Thus, for example, a different sequence of events was investigated involving, in a model study, linking the substrates **40** and boronic ester **43** first to give tricycle **51** (Scheme 2.10), followed by removal of the Boc-group and *N*-alkylation with 3,4-dimethoxyphenethylbromide (**12**) and thus affording the tricyclic compound **42**. The outcomes of pursuing this approach are shown in Scheme 2.10.



Scheme 2.10: Alternative Route to Ningalin B *Reagents and conditions:* a) $Pd(PPh_3)_4$, K_2CO_3, 70 °C, 1 h, 78%; b) $ZnBr_2$, 18 °C, 20 h, 93%; c) **12**, NaH, 18 °C, 4 h, 78%.

While the NMR spectral data obtained on product **51** were completely consistent with the assigned structure, final confirmation of this followed from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 2.5.

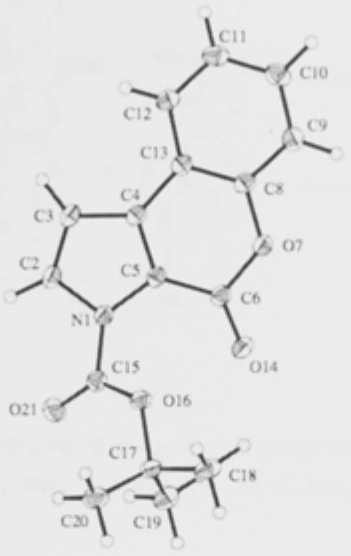
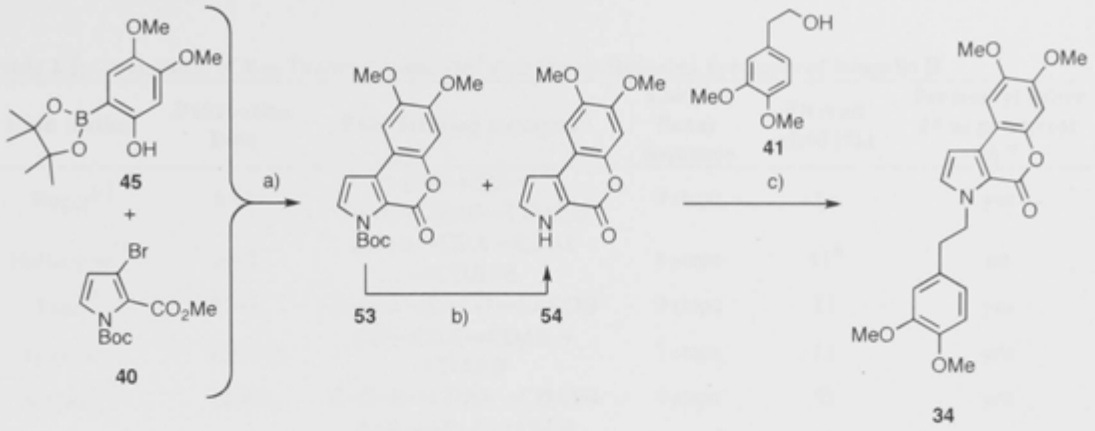


Figure 2.5: Molecular Structure of Compound **51** ($C_{16}H_{19}NO_4$) with Labelling of Selected Atoms (anisotropic displacement ellipsoids show 30% probability levels; hydrogen atoms are drawn as circles with small radii).

This approach improved the yield of the sequence **40** → **42** from 52% to 56%. It was anticipated that this new route would also provide a better outcome when used with the fully functionalised boronic ester required for the synthesis of ningalin B. Accordingly, the linking of substrates **40** and **45** by such means was studied and this allowed for the preparation of lactone **53** in 55% yield (Scheme 2.11). Product **53** was accompanied by *ca.* 14% of the deprotected pyrrole **54**. Removal of the Boc group within the still protected compound **53** was readily achieved in 84% yield using zinc bromide and the resulting pyrrole **54** was *N*-alkylated with alcohol **41** under Mitsunobu conditions and thus affording lactone **34** in 54% yield. Despite these efforts, the yield of target **34** obtained using the route shown in Scheme 2.11 was only marginally better than that observed earlier (33% versus 27%).



Scheme 2.11: Alternative Route to Ningalin B *Reagents and conditions:* a) $Pd(PPh_3)_4$, Cs_2CO_3, 70 °C, 1 h, 55% (and 14% **54**); b) $ZnBr_2$, 18 °C, 3 h, 84%; e) DIAD, PPh_3, 18 °C, 30 h, 54%.

2.4 Summary and Conclusions

A comparison of the key features associated with all of the reported syntheses of ningalin B, including the present work, is provided in Table 2.3. The Steglich[7] and Bullington[5] syntheses are the shortest (each involves just four steps) and particularly notable for their efficiency. The Steglich synthesis[7] is remarkable for the rapidity with which the basic framework of the target compound is assembled but the Bullington approach is likely to be the more effective for preparing analogues of ningalin B in which the substituents on the C and D rings are different. It is also worth noting that the Bullington, [5] Boger[2] and Gupton[8] syntheses share a common sequence of ring-forming events (Table 2.3) and that this is related to the one used by Steglich and co-workers. These involve a mid-stage pyrrole-forming step while the construction of the B-ring lactone is left to the end of the synthetic sequence. In contrast, the synthesis of target **7** reported herein starts with an intact pyrrole and uses this ring system as a template for introducing the remaining structural components of ningalin B. While the present approach is not as efficient as some of the others described to date, it should be particularly useful for the preparation of ningalin B analogues in which the substitution patterns associated with the C, D and E rings are quite different from one another.

Table 2.3: Comparison of Key Features Associated with the six Reported Syntheses of Ningalin B

Lead Author	Publication Date	Ring-forming sequence[A]	Longest linear sequence	Overall yield [%]	Permethyl Ether 14 as precursor to 7
Boger[2]	2000	C+D→CD→ CDA→CDAE→CDAEB	9 steps	16	yes
Bullington[5]	2002	CD+A→CDA→CDAE →CDAEB	4 steps	41[B]	no
Iwao[6]	2003	E→EA→EACD→EACDB	9 steps	11	yes
Gupton[8]	2009	CD→CDA→CDAE→ CDAEB	7 steps	13	yes
Steglich[7]	2006	C+D+E→CDAE→CDAEB	4 steps	52	yes
Present work	2009	A+E→AE+C→AECB →AECBD	7 steps[C]	17	yes

[A] See Figure 2.1 for labelling of the ring system associated with ningalin B.
[B] For the purposes of this calculation it has been assumed that the first step of the sequence, leading to the required α,β-unsaturated nitrile, proceeds in 80% yield.
[C] Step count starts from compound **36**.

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3 Synthetic Investigations into the Biogenesis of the Pentacyclic Lamellarin Framework

3.1 Previous Approaches Used in Assembling the Pentacyclic Lamellarin Framework 51

3.2 First Generation Approach to Lamellarin G Trimethyl Ether 60

3.2.1 Retrosynthetic Analysis 60

3.2.2 Results and Discussion 61

3.2.3 An Unusual Ring-closing Reaction and its Implications for Mimicking the Biogenesis of the Pentacyclic Lamellarins 63

3.3 Second Generation Approach to Lamellarin G Trimethyl Ether 65

3.3.1 Retrosynthetic Analysis 65

3.3.2 Results and Discussion 67

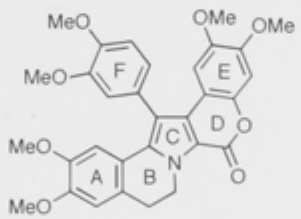
3.4 Summary and Conclusions 79

3.5 References 80

3 Synthetic Investigations into the Biogenesis of the Pentacyclic Lamellarin Framework

The primary focus of the work detailed in this Chapter arose from some unexpected observations made during efforts to assemble the pentacyclic lamellarin framework using intermediates associated with the synthesis of ningalin B. Thus, during the course of the studies detailed below certain novel reactions were encountered that, while thwarting the original plans, prompted the idea that a biomimetic synthesis of the aforementioned framework could be established.

The difficulty associated with synthesising the pentacyclic lamellarins lies in the construction of the associated framework. Since the early 1990's a number of different strategies have been implemented to construct the ABCDE ring-system (Figure 3.1). A representative selection of these is presented below. For the purposes of simplification, this selection focuses on the synthesis of lamellarin G trimethyl ether **55** that has been and continues to represent a popular target for research groups working in the area.

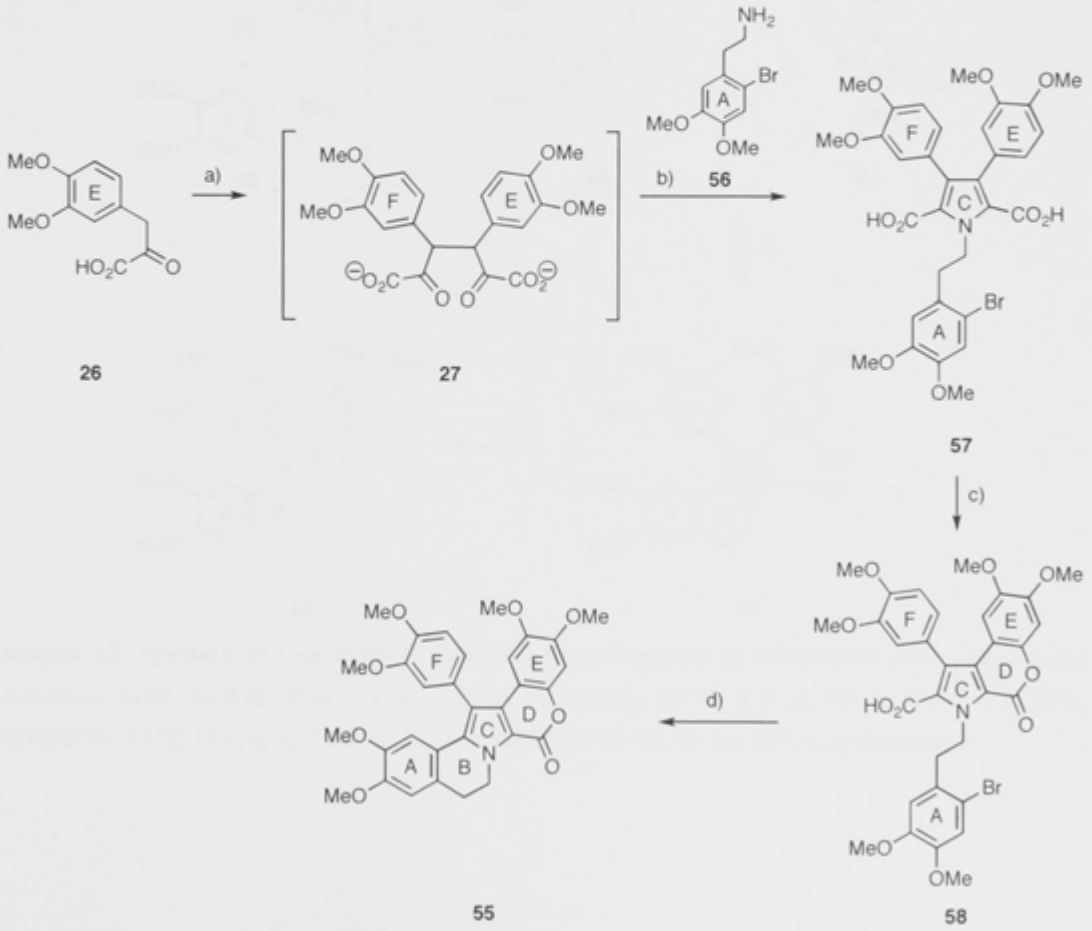


55

Figure 3.1: The Structure of Lamellarin G Trimethyl Ether

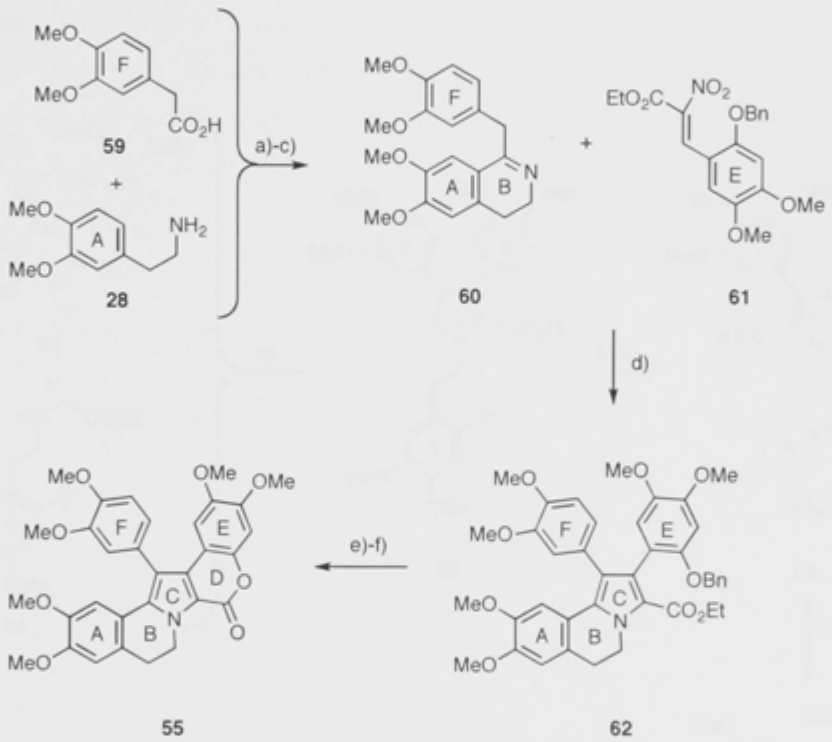
3.1 Previous Approaches Used in Assembling the Pentacyclic Lamellarin Framework

Steglich and coworkers[1] were the first to construct the pyrrole core of lamellarin G trimethyl ether and did so in a biomimetic fashion (Scheme 3.1). The early stages involved the oxidative coupling of two molecules of aryl pyruvic acid **26**. This provided the 1,4-diketone **27** that reacted, *in situ*, with 2-arylethylamine **56** to provide the *N*-substituted pyrrole **57**. Lead-tetraacetate-mediated lactonisation of compound **57** afforded product **58** and the final ring-forming process utilised a novel decarbonylative Heck reaction to produce the target molecule **55**. In summary, then, the ring-forming events follow the sequence E + F → EF + A → EFAC → EFACD → EFACDB.



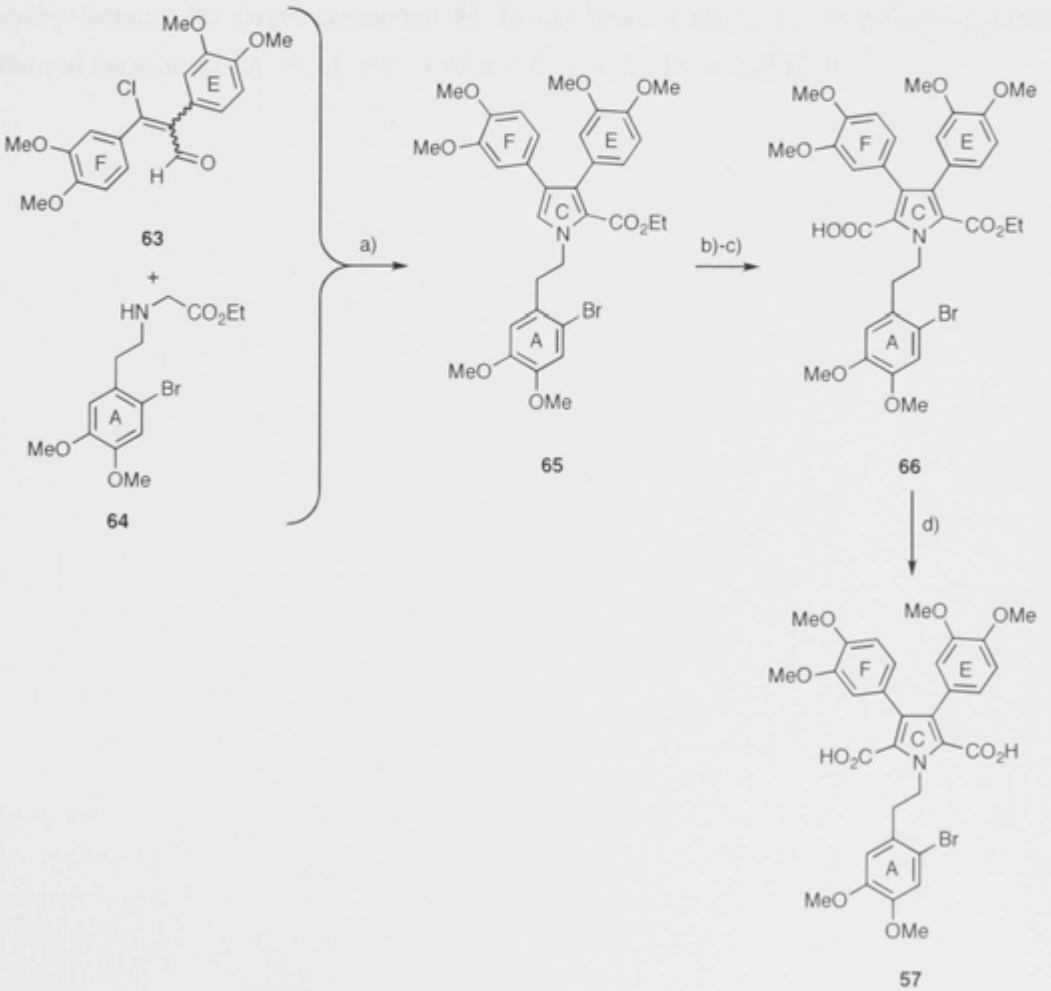
Scheme 3.1: Synthesis of Lamellarin G Trimethyl Ether Reported by Steglich *et al.* *Reagents and conditions:* a) *n*-BuLi (2.0 eq.), I_2 (0.5 eq.), −70→25 °C, 2 h; b) **56**, molecular sieves (4Å), 25 °C, 12 h, 62% (over two steps); c) $Pb(OAc)_4$, 77 °C, 3 h, 71%; d) $Pd(OAc)_2$, PPh_3, NEt_3, 82 °C, 18 h, 74%.

Ruchirawat's synthesis,[2] depicted in Scheme 3.2, involved an initial amide-forming step involving aryl ethylamine **28** and the acid **59**. The product of this process was subjected to a Bischler-Napieralski reaction and thus producing benzylhydroisoquinoline **60**. Condensation of the latter with α–nitrocinnamate **61** gave, *via* a base-mediated Michael-addition/ring closing reaction sequence, the pentacyclic pyrrole **62** that, through a series of standard reactions, was finally converted into lamellarin G trimethyl ether. The ring-forming events associated with Ruchirawat's synthesis follow the sequence ABF + E → ABFEC → ABFECD.



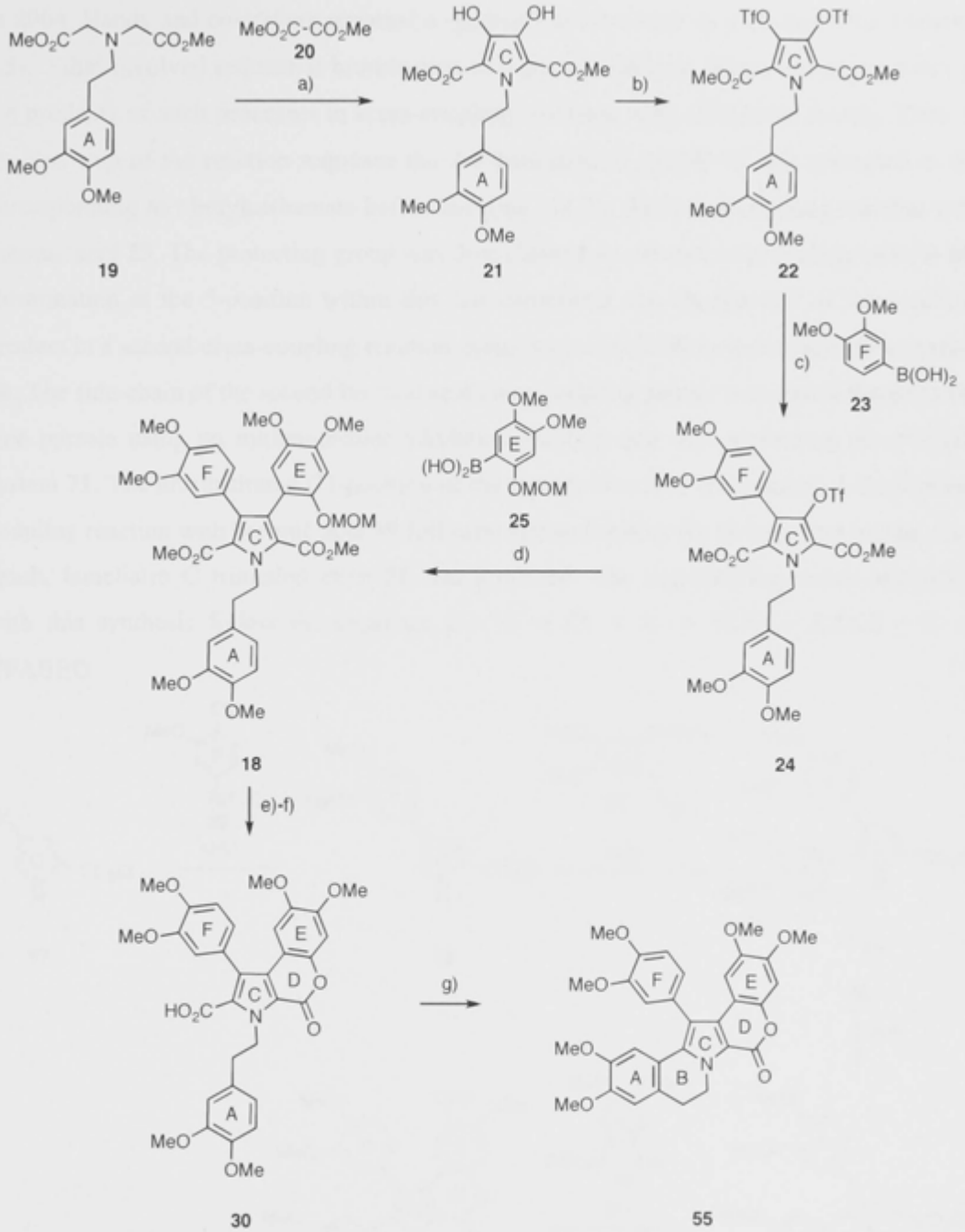
Scheme 3.2: Synthesis of Lamellarin G Trimethyl Ether Reported by Ruchirawat *et al.* *Reagents and conditions:* a) **59**, $(COCl)_2$, DMF, 25 °C, 2 h; b) **28**, Na_2CO_3, 25 °C, 2 h; c) $POCl_3$, 25 °C, 3 h, 84%; d) $NaHCO_3$, 82 °C, 18 h; e) H_2, Pd/C, 25 °C, 24 h; f) NaH, 0 °C→25 °C, 4 h, 52% (over three steps).

Gupton and coworkers[3] developed a synthesis of compound **57**, a key and late-stage intermediate associated with the Steglich route, and thereby providing a formal synthesis of lamellarin G trimethyl ether. Details of the approach are shown in Scheme 3.3. This starts with condensation of β-chloroenal **63** and the *N*-substituted glycine derivative **64** and thus forming compound **65** incorporating a pyrrole ring with the appropriate substitution at C3 and C4. Subjection of pyrrole **65** to a Vilsmeier-Haack-Arnold reaction followed by Pinnick-oxidation of the ensuing pyrrole 2-carboxaldehyde afforded acid **66**. Saponification of the ethyl ester moiety within this last compound then furnished the 'Steglich intermediate' **57**. The ring-forming events used by Gupton follow the sequence EF + A → EFAC → EFACD → EFACDB.



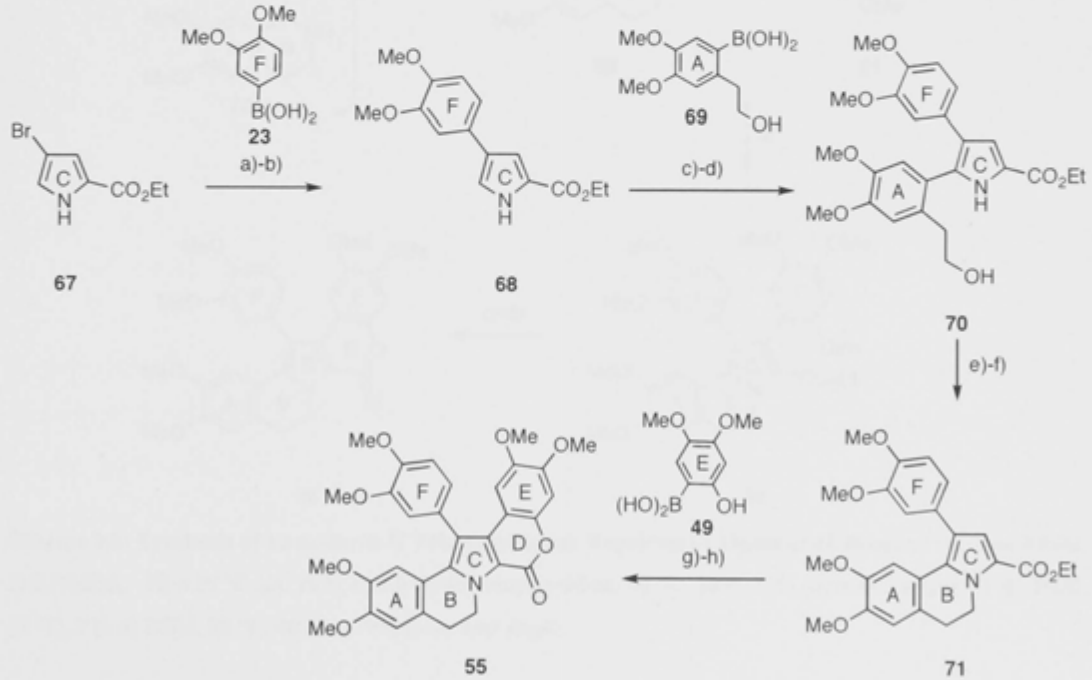
Scheme 3.3: Formal Synthesis of Lamellarin G Trimethyl Ether Reported by Gupton *et al.* *Reagents and conditions:* a) 150 °C (μ-wave heating), 3 h, 83%; b) $POCl_3$, DMF, 100 °C (μ-wave heating), 7 min, 92%; c) $NaClO_2$, 25 °C, 20 h, 84%; d) KOH/H_2O, 80 °C, 70 h, 96%.

In developing their synthesis of lamellarin G trimethyl ether Iwao and coworkers[4] utilised an approach previously exploited in the preparation of ningalin B (see Chapter 2). Thus, a Hinsberg-type condensation reaction (Scheme 3.4) of the iminodiacetate **19** with dimethyl oxalate **20** produced the symmetrical pyrrole-dicarboxylate **21** that was then converted into the *bis*-triflate **22** using standard procedures. This was, in turn, subjected to a Suzuki-Miyaura cross-coupling reaction with one equivalent 3,4-dimethoxyphenylboronic acid **23** and thus affording the desymmetrised pyrrole **24**. A second cross-coupling reaction followed and so giving the MOM-protected compound **18**. The lactonisation of compound **18** was achieved by acid-mediated deprotection of the methoxymethyl group and this was followed by spontaneous cyclisation of the unmasked hydroxy ester to give pyrrole **30**. The final, ring-closing step involved a modification of Steglich's decarbonylative Heck reaction, and thereby forming the target compound **55**. In the Iwao synthesis the ring-forming events followed the sequence A → AC + F → ACF + E → ACFED → ACFEDB.



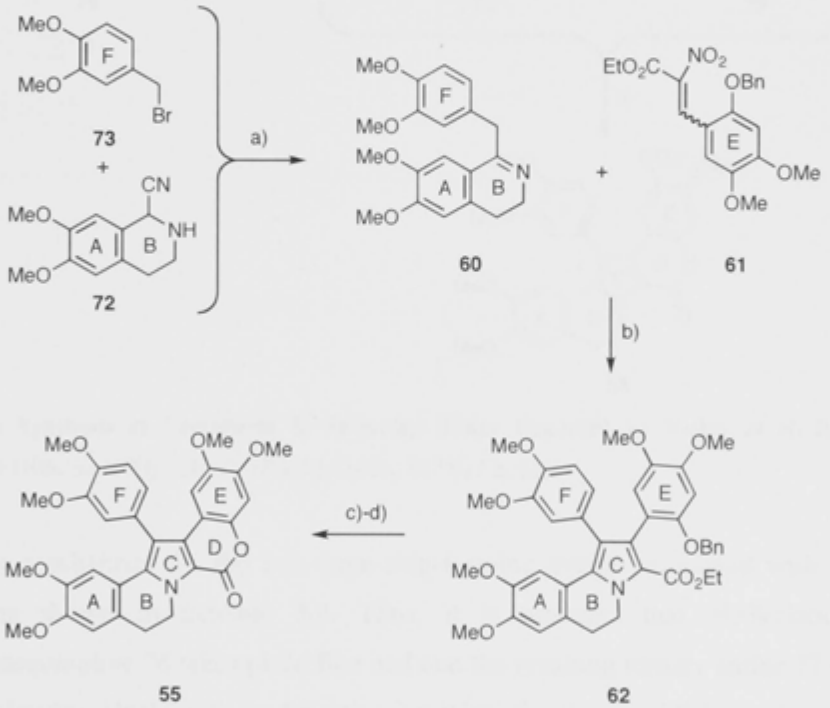
Scheme 3.4: Synthesis of Lamellarin G Trimethyl Ether Reported by Iwao *et al.* *Reagents and conditions:* a) **20**, MeONa, 65 °C, 18 h, 49%; b) $(CF_3SO_2)_2O$, 0 °C, 2 h, 87%; c) **23** (1.0 eq.), $Pd(PPh_3)_4$, aq. Na_2CO_3, 66 °C, 4 h, 78%; d) **25** (2.0 eq.), $Pd(PPh_3)_4$, aq. Na_2CO_3, 66 °C, 20 h, 58%; e) HCl, 66 °C, 1 h, 90%; f) i) 40% aq. KOH, 110 °C, 3 h; ii) cat. *p*-TsOH, 110 °C, 30 min, 76%; g) $Pd(OAc)_2$, 82 °C, 12 h, 65%.

In 2004, Handy and coworkers reported a synthesis of lamellarin G trimethyl ether (Scheme 3.5),[5] that involved sequential bromination of a pyrrole building block and engagement of the products of such processes in cross-coupling reactions with substituted arenes. Thus, in the first step of the reaction sequence the 2,4-disubstituted pyrrole **67** was protected as the corresponding *tert*-butylcarbamate before carrying out the first cross-coupling reaction with boronic acid **23**. The protecting group was then cleaved *in situ* and so producing pyrrole **68**. Bromination at the 5-position within this last compound and engagement of the resulting product in a second cross-coupling reaction using boronic acid **69** then produced free pyrrole **70**. The side-chain of the second boronic acid cross-coupling partner was now tethered to the free pyrrole using an intramolecular alkylation reaction and thus producing the tricyclic system **71**. The unsubstituted C3-position of the pyrrole was then brominated. A third cross-coupling reaction with boronic acid **49** followed and so forming the lactone ring *in situ*. As a result, lamellarin G trimethyl ether **55** was produced. The ring-forming events associated with this synthesis follow the sequence C + F → CF + A → CFA → CFAB + E → CFABED.



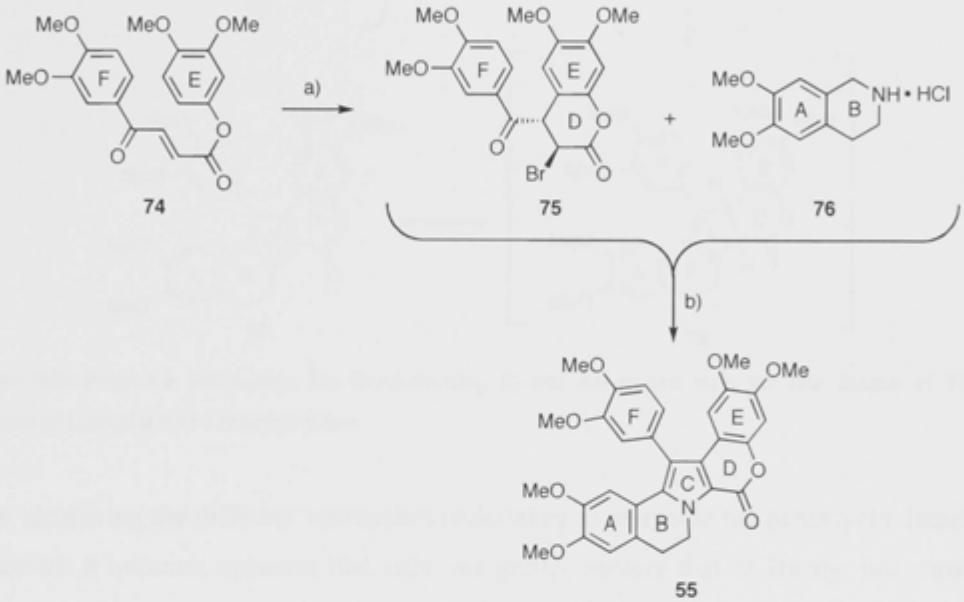
Scheme 3.5: Synthesis of Lamellarin G Trimethyl Ether Reported by Handy *et al.* *Reagents and conditions:* a) $(Boc)_2O$, DMAP, 20 °C, 1 h, 93%; b) **23**, $Pd(PPh_3)_4$, aq. Na_2CO_3, 110 °C, 15 h, 70%; c) NBS, 0→20 °C, *ca.* 16 h, 100%; d) **69**, $Pd(PPh_3)_4$, aq. Na_2CO_3 110 °C, 15 h, 54%; e) *p*-TsCl, pyr, 0→20 °C, *ca.* 16 h, 62%; f) NaH, 20 °C, 2 h, 98%; g) NBS, 0→20 °C, *ca.* 16 h, 100%; h) **49**, $Pd(PPh_3)_4$, aq. Na_2CO_3 110 °C, 5 h, 46%.

Opatz's synthesis of lamellarin G trimethyl ether was reported in 2008[6] and the essential elements of this are shown in Scheme 3.6. The route used is similar to that of Ruchirawat.[2] Thus, Opatz also used benzylhydroisoquinoline **60** as a key intermediate, although this was synthesised *via* alkylation of the conjugate base derived from α-aminonitrile **72** with benzylic bromide **73**. This permitted the introduction of acid-sensitive protecting groups onto the tricyclic fragment. A Grob reaction between product **60** and an *E*/*Z*-mixture of nitrocinnamate **61** then gave the pyrrole **62** that was deprotected and then subjected to lactonisation conditions so as to form the D-ring and thereby complete the synthesis of lamellarin G trimethyl ether. The ring-forming events associated with this synthesis follow the sequence AB + F → ABF + E → ABFEC → ABFECD.



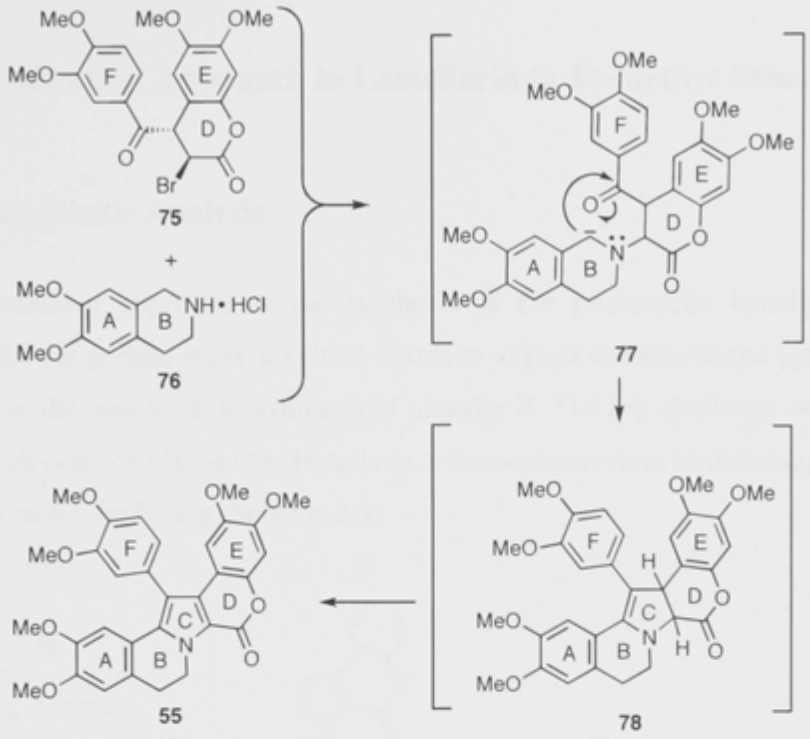
Scheme 3.6: Synthesis of Lamellarin G Trimethyl Ether Reported by Opatz *et al.* *Reagents and conditions:* a) KHMDS, –78→25 °C, *ca.* 16 h; b) 2,6-di-*tert*-butylpyridine, 90 °C, 20 h, 42% (over two steps); c) H_2, Pd/C, 25 °C, 2 h; d) DBU, 80 °C, 40 min, 79% (over two steps).

The last and most efficient synthesis of the lamellarin framework was published by Yadav *et al.* in 2009[7] and the reaction sequence involved is shown in Scheme 3.7. Thus, the ester **74**, previously reported by Neises and Steglich,[8] was prepared in two steps from commercially available starting materials. Brominative arylation of this compound produced chromanone **75** that was subjected to coupling with isoquinoline **76** and, through a series of spontaneous reactions, this gave lamellarin G trimethyl ether (**55**).



Scheme 3.7: Synthesis of Lamellarin G Trimethyl Ether Reported by Yadav *et al.* *Reagents and conditions:* a) NBS, $Sm(OTf)_3$, 20 °C, 93%; b) K_2CO_3, 82 °C, 2 h, 63%.

A plausible mechanism for the late-stage ring-forming events associated with the Yadav synthesis is shown in Scheme 3.8. Thus, it is assumed that *N*-alkylation of the tetrahydroisoquinoline **76** takes place first and that the resulting tertiary amine **77** engages in an intramolecular aldol-type condensation reaction thereby establishing the pentacyclic intermediate **78**. Subsequent (*in situ*) aromatisation (by aerial oxidation) then follows and affords the target pyrrole **55**. The ring-forming events associated with the Yadav synthesis follow the sequence E + F → EF → EFD + AB → EFDABC.



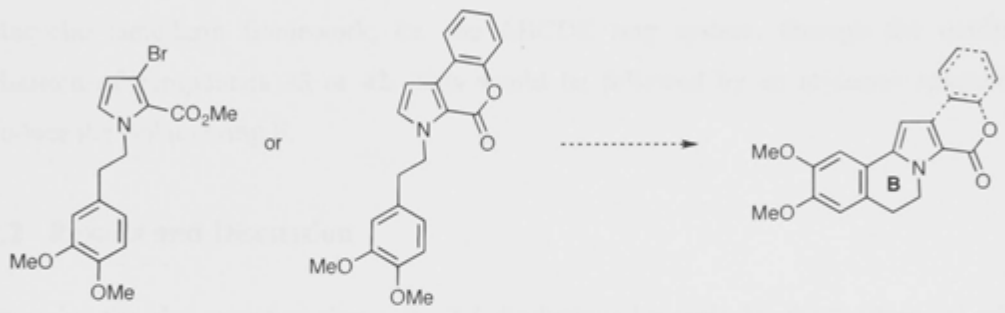
Scheme 3.8: Proposed Mechanism for Bond-forming Events Associated with the late Stages of Yadav's Synthesis of Lamellarin G Trimethyl Ether.

When comparing the different approaches undertaken to assemble the pentacyclic lamellarin framework it becomes apparent that only one group, namely that of Handy, has chosen to commence with a pyrrole centrepiece, *i.e.* an intact C-ring. As already discussed in Chapter 2, the lack of focus on such an approach to the pentacyclic lamellarins framework is probably due to the challenges involved in effecting regioselective halogenation and cross-coupling reactions of pyrroles.

3.2 First Generation Approach to Lamellarin G Trimethyl Ether

3.2.1 Retrosynthetic Analysis

The first generation approach to the synthesis of the pentacyclic lamellarin skeleton associated with the present work involved efforts to exploit the substituted pyrroles **35** and **42** generated in the course of the synthesis of ningalin B. The key challenge associated with converting such compounds into the lamellarin framework involves establishing an effective method for creating the B-ring (Scheme 3.9).



35 **42** **79**

Scheme 3.9: Pivotal Cyclisation Reaction Associated with the Proposed First Generation Approach to the Synthesis of the Pentacyclic Lamellarins.

Previous studies by Banwell and coworkers[9] suggested that by using a combination of phenyliodine(III) *bis*(trifluoroacetate) (PIFA) and boron trifluoride diethyl etherate (Scheme 3.10) compounds such as **35** and **42** could undergo the required cyclisation and thus forming the targeted B-ring of the framework **79**. Specifically, this group had shown that by subjecting pyrrole **80** or 3,4-diphenylpyrrole **81** to this reagent combination these could be converted into the pyrroloisoquinolines **82** and **83**, respectively. This type of methodology was originally developed and deployed by Kita and coworkers[10] and applied to pyrrolic substrates by Tellitu *et al.*[11]

80 R = H
81 R = Ph

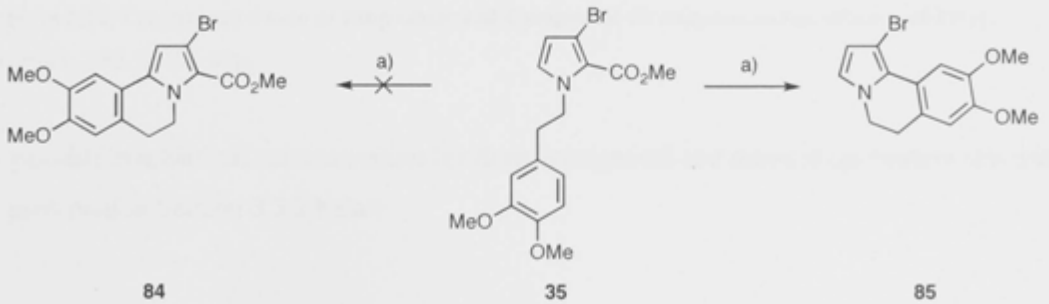
82 R = H
83 R = Ph

Scheme 3.10: Precedence for B-ring Closure Reaction from the Banwell Group *Reagents and conditions:* a) PIFA [phenyliodine(III) *bis*(trifluoroacetate)], BF_3•OEt_2, –40 °C, 3 h, for R = H 24%, for R = Ph 40%.

Given this precedence, it seemed reasonable to contemplate establishing a synthesis of the pentacyclic lamellarin framework, *i.e.* the ABCDE ring system, through the oxidative cyclisation of compounds **35** or **42**. This would be followed by an arylation reaction to introduce the isolated ring F.

3.2.2 Results and Discussion

In pursuing the plan specified above, the 2,3-disubstituted pyrrole **35**, the synthesis of which was described in Chapter 2, was subjected to reaction with PIFA/BF_3•Et_2O under the conditions employed earlier. While a cyclisation reaction took place, the desired compound **84** was not formed (Scheme 3.11). Rather, the reaction resulted in loss of the ester moiety and a fused ring system was formed at the 2-position and thereby giving bromide **85** (29%), the structure of which followed from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 3.2.



84 **35** **85**

Scheme 3.11: Unexpected Mode of Ring-closure of Compound 35 *Reagents and conditions:* a) PIFA, BF_3•OEt_2, –40 °C, 3 h, 29%.

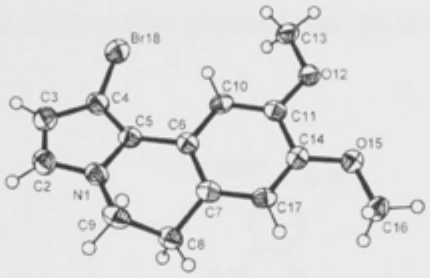
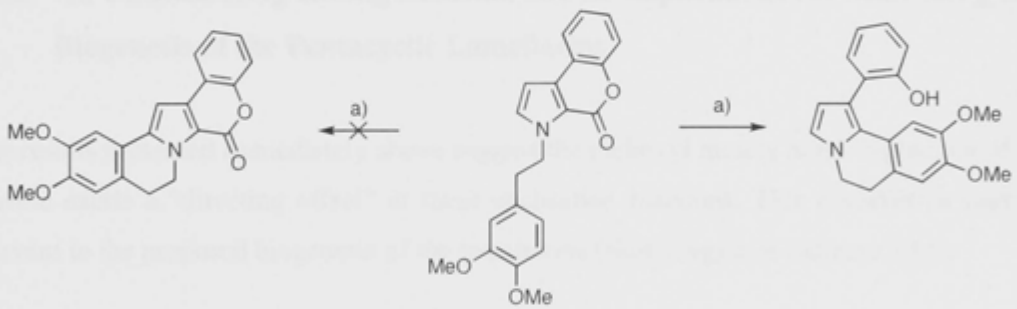


Figure 3.2: Molecular Structure of Compound **85** ($C_{14}H_{14}BrNO_2$) with Labelling of Selected Atoms. (anisotropic displacement ellipsoids show 50% probability levels; hydrogen atoms are drawn as circles with small radii).

In an attempt to avoid the problems encountered above, the previously synthesised lactone **42** was employed as a substrate (Scheme 3.12) in the PIFA/BF_3•Et_2O reaction. However, the same problem occurred and instead of forming the desired pentacycle **86**, the only isolable product of this reaction was the tricyclic pyrrole **87** (9%).

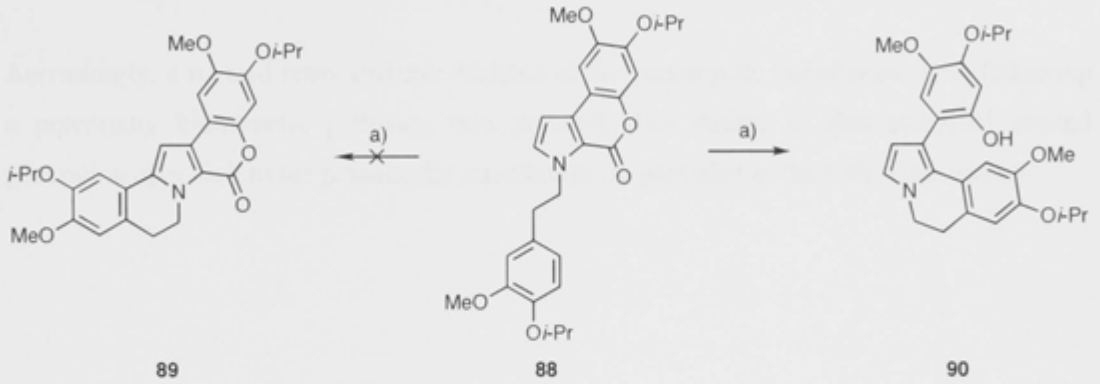


86 **42** **87**

Scheme 3.12: Unexpected Mode of Ring-closure of Compound 42 *Reagents and conditions:* a) PIFA, BF_3•OEt_2, –40 °C, 3 h, 9%.

A possible mechanistic rationalisation for these unexpected and unusual cyclisation reactions is presented in Section 3.3.2 below.

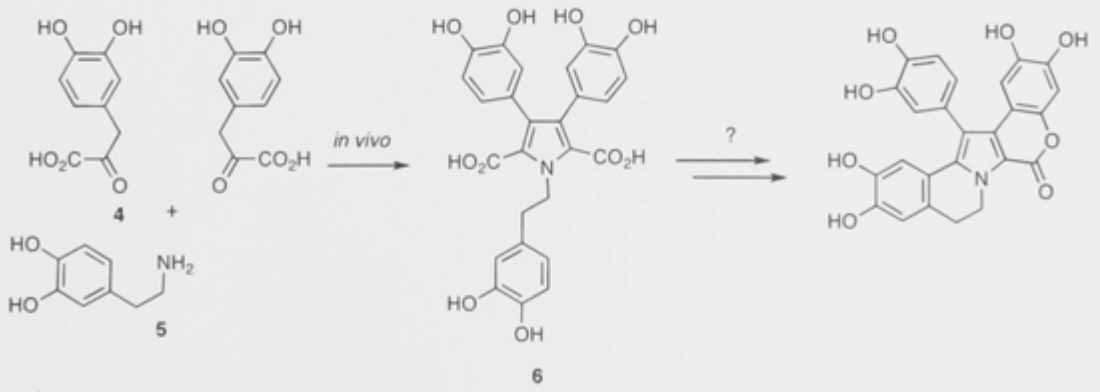
The type of cyclisation reaction shown in Schemes 3.11 and 3.12 was also observed by Iwao and coworkers[12] during their attempts to assemble the pentacyclic lamellarin framework from tricyclic pyrrole **88** (Scheme 3.13). Thus, instead of forming desired pentacyclic pyrrole **89**, the only isolable product they obtained was the tricyclic species **90**. This was formed in 49% yield.



Scheme 3.13: Unusual Mode of Ring-closure observed by Iwao and coworkers *Reagents and conditions:* a) PIFA, BF_3•OEt_2, –40 °C, 2 h, 49%.

3.2.3 An Unusual Ring-closing Reaction and its Implications for Mimicking the Biogenesis of the Pentacyclic Lamellarins

The results presented immediately above suggest the carboxyl moiety at the 2-position of the pyrrole exerts a "directing effect" in these cyclisation reactions. This observation may be relevant to the proposed biogenesis of the lamellarins (shown again in Scheme 3.14).



Scheme 3.14: Proposed Biogenesis of the Simple and Complex Lamellarins

Thus, and as noted before, in this process two molecules of pyruvic acid **4** and one of 3,4-hydroxyphenethyl amine **5** engage in an oxidative coupling reaction/condensation sequence, to give the symmetrically tetrasubstituted pyrrole **6** as the progenitor to the lamellarin-type alkaloids. Pyrrole **6** has carboxylic acid groups at the C2- and C5-positions and given the experimental observations reported above, it is likely that the carboxyl moieties play an important role in the biogenesis of the lamellarins.

Accordingly, a revised retrosynthetic analysis of the pentacyclic lamellarins, now following a potentially biomimetic pathway, was pursued. The details of this so-called second generation approach to the pentacyclic lamellarins are provided in the following section.

3.3 Second Generation Approach to Lamellarin G Trimethyl Ether

The initial investigations into the development of a biomimetic synthesis of the pentacyclic lamellarins focussed on establishing a synthesis of lamellarin G trimethyl ether **55**. The choice of this compound as the primary target derived from the simplifications to the synthesis arising from avoiding the need to establish a combination of methoxy and hydroxy substituents around the periphery of this pentacyclic framework.

3.3.1 Retrosynthetic Analysis

The retrosynthetic analysis of lamellarin G trimethyl ether **55** shown in Figure 3.3 is based on the unexpected PIFA-mediated cyclisation discussed earlier and involves using compound **91** as the substrate for this pivotal reaction. Thus, it was expected that upon exposure to PIFA/BF_3•Et_2O this would result in cleavage of the C5-carbomethoxy group within the substrate and the formation of lamellarin G trimethyl ether. Of course, given the results reported earlier (Section 3.2.2), it is also possible that the reaction would lead to cleavage of the lactone ring and formation of the alternate cyclisation product. The outcome of efforts to explore such matters is reported below.

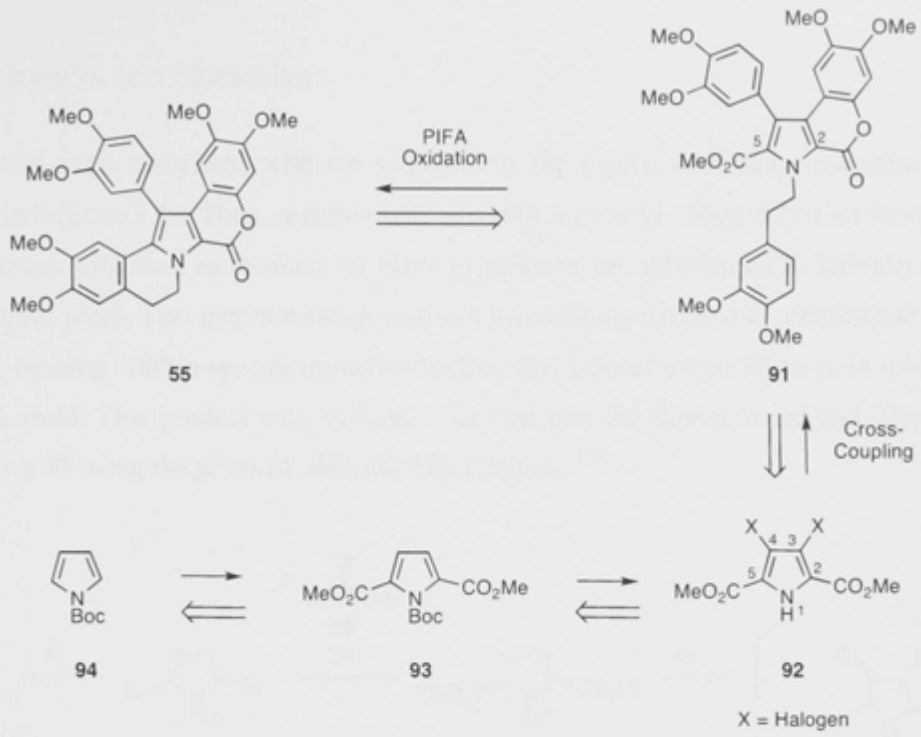


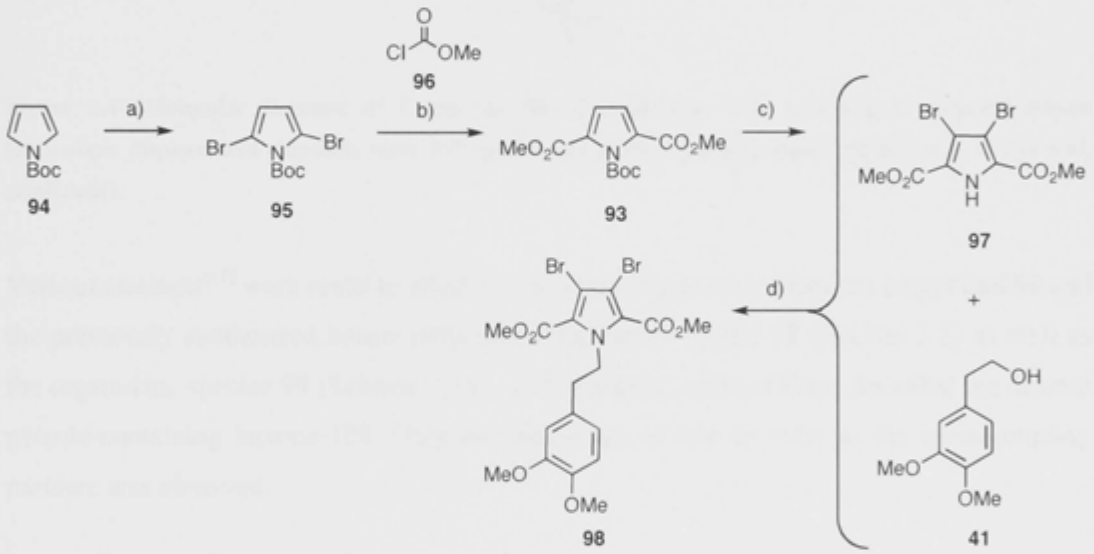
Figure 3.3: Second Generation Retrosynthetic Analysis of the More Complex Lamellarins Based on a Biomimetic Approach

Pentacyclic pyrrole **91** was thought to be derivable from precursor **92** *via* an alkylation and cross-coupling sequence. Due to its versatility, compound **92** is one of the key entities described in this Chapter as it contains functional groups that should be easily manipulated so as to deliver the pentacyclic lamellarin natural products.

In principle, and by using the cross-coupling methodology discussed earlier (see Chapter 2), compound **92** can be functionalised at the C3- and C4-positions of the pyrrole ring. Furthermore, the ester-functionalities at C2 and C5 can be saponified, *trans*-esterified and/or lactonised. Finally, alkylation at N1 would introduce the required 3,4-dimethoxyphenethyl moiety associated with most of the lamellarins. Structure **92** was thought likely to be accessible from the known compound **93** which has itself been synthesised from *tert*-butyl 1*H*-pyrrole-1-carboxylate (**94**).[13]

3.3.2 Results and Discussion

The initial steps associated with the synthesis of the pivotal cyclisation substrate **91** are shown in Scheme 3.15. Thus, commercially available *tert*-butyl 1*H*-pyrrole-1-carboxylate **94** was treated with two equivalents of NBS to produce the dibrominated derivative **95** in quantitative yield. This unstable compound was immediately exposed to *tert*-BuLi at –78 °C and the ensuing dilithio-species quenched with methyl chloroformate **96** to yield tri-ester **93** in 58% yield. This product was, in turn, converted into the dibrominated and deprotected derivative **97** using the protocols described by Fürstner.[13]



Scheme 3.15: Synthesis of 3,4-Dibromopyrrole 98 *Reagents and conditions:* a) NBS, –78→18 °C, *ca.* 16 h, quantitative; b) *tert*-BuLi, then **96**, –78→18 °C, *ca.* 16 h, 58%; c) Br_2, 18 °C, 5 min, 99%; d) DIAD, PPh_3, 18 °C, 14 h, 69%.

Subjection of compound **97** to a Mitsunobu reaction[14] using 3,4-dimethoxyphenethyl alcohol **41** produced 3,4-dibromopyrrole **98** in 69% yield. The NMR spectral data obtained on this product were completely consistent with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 3.4.

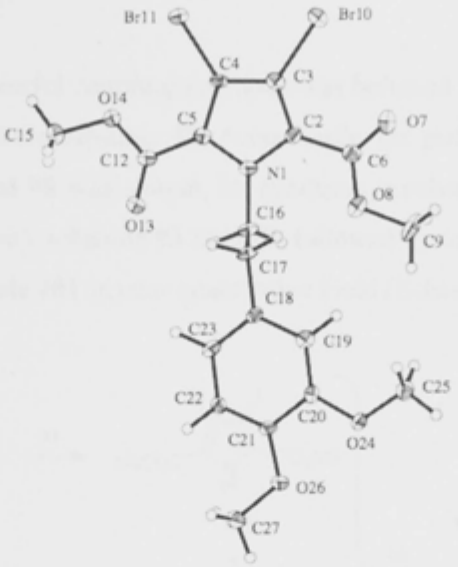
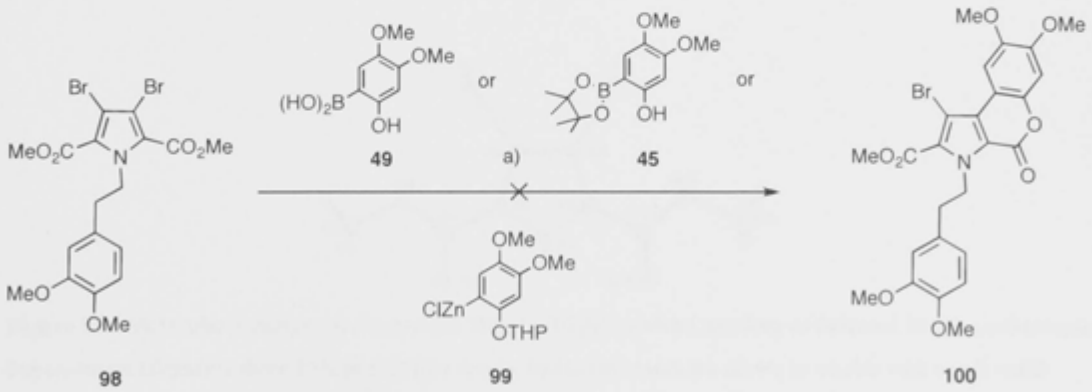


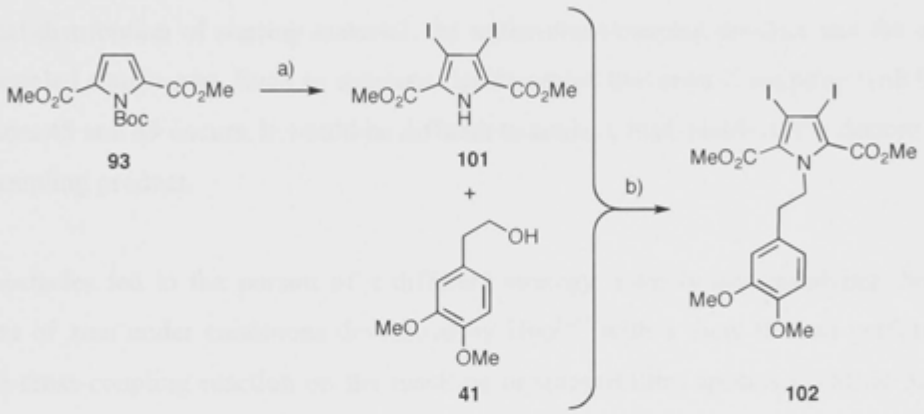
Figure 3.4: Molecular Structure of Compound **98** ($C_{18}H_{19}BrNO_6$) with Labelling of Selected Atoms (anisotropic displacement ellipsoids show 30% probability levels; hydrogen atoms are drawn as circles with small radii).

Various attempts[15] were made to effect a cross-coupling reaction between compound **98** and the previously synthesised boron-containing compounds **45** and **49** (Section 2.2) as well as the organozinc species **99** (Scheme 3.16). Unfortunately, none of these provided the desired pyrrole-containing lactone **100**. Only decomposition of one or other of the cross-coupling partners was observed.



Scheme 3.16: Attempted Synthesis of Cross-coupled Product 100 *Reagents and conditions:* a) catalysts: $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$; heating conditions: 70 °C, 100 °C or 110 °C , microwave and conventional heating; bases: Na_2CO_3, K_2CO_3; no product observed, only decomposition.

The origin of these unsuccessful coupling-reactions was believed to be the low reactivity of the bromine-containing pyrrole substrate **98**. Accordingly, the potentially more reactive *bis*-iodo-analogue of compound **98** was sought. Its synthesis involved thermal deprotection of the Boc-group associated with substrate **93** in DMF followed by *in situ* addition of NIS. This produced the *bis*-iodo-pyrrole **101** in near quantitative yield (Scheme 3.17).



Scheme 3.17: Synthesis of 3,4-Diiodopyrrole 102 *Reagents and conditions:* a) 130 °C, 12 h, then 80 °C, NIS, 4 h, 97%; b) DIAD, PPh_3, 18 °C, 14 h, 88%.

While all spectral data derived from compound **101** were in complete accord with the assigned structure, final confirmation of this came from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 3.5.

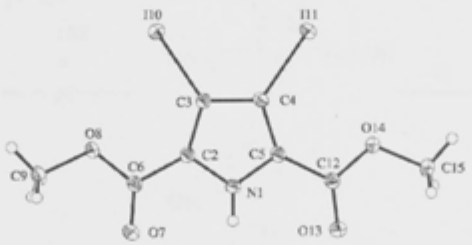


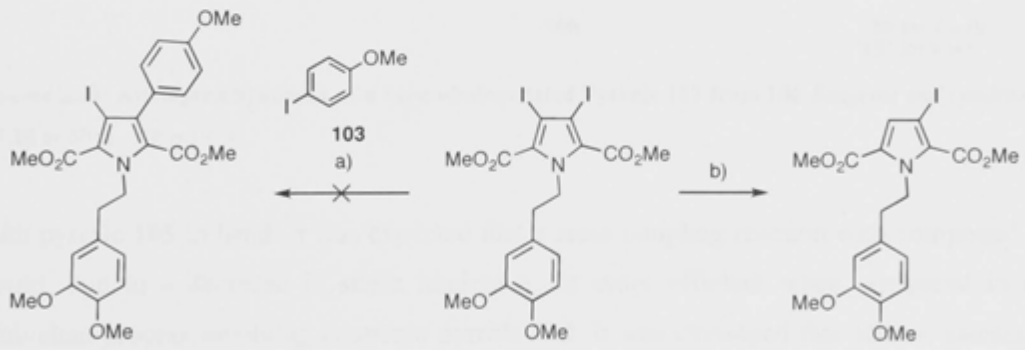
Figure 3.5: Molecular Structure of Compound **101** ($C_8H_7I_2NO_4$) with Labelling of Selected Atoms (anisotropic displacement ellipsoids show 30% probability levels; hydrogen atoms are drawn as circles with small radii).

Alkylation of *bis*-iodide **101** with alcohol **41** under the sorts of Mitsunobu conditions described previously furnished pyrrole **102** in excellent yield (Scheme 3.17).

Unfortunately, every attempt to obtain satisfactory yields of the target diarylated pyrrole by cross-coupling of di-iodide **102** with an appropriate boronic acid or the corresponding boronate ester failed. Only decomposition of the boron-containing substrates was observed.

In order to study the ability of compound **102** to undergo mono-coupling, and thus desymmetrisation, *bis*-iodo-pyrrole **102** was treated with the much more reactive and commercially available 3,4-dimethoxyphenyl boronic acid. The coupling proceeded with high conversion, however, if only one equivalent of the boronic acid was used, this led to a statistical distribution of starting material, the mono-cross-coupled product and the doubly-cross-coupled counterpart. Such an outcome demonstrated that even if coupling with boronic precursors **45** and **49** occurs, it would be difficult to achieve high yields of the desired mono-cross-coupling product.

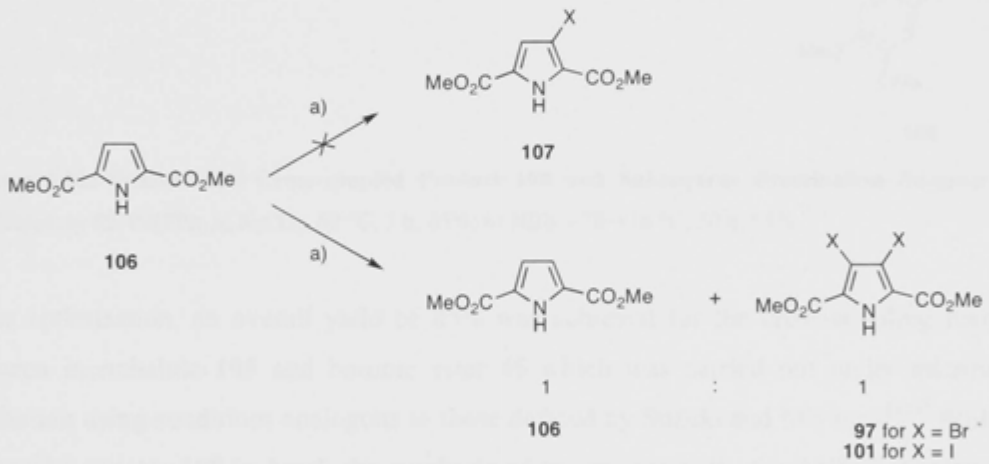
Such obstacles led to the pursuit of a different strategy, namely one involving the direct insertion of zinc under conditions developed by Huo[16] with a view to then performing a Negishi-cross-coupling reaction on the resulting organometallics species (Scheme 3.18). In the event, strong evidence for a successful zinc-insertion was obtained, since approximately 60% of the reaction mixture contained deiodinated product. However, only a small percentage (~5%) of this species actually participated with a cross-coupling reaction when *p*-iodoanisol **103** was used as a coupling partner.



Scheme 3.18: Synthesis of Desymmetrised Pyrrole 105 *Reagents and conditions:* a) Zn, I_2 [cat.], **103**, $Pd(PPh_3)_4$, 80 °C, 12 h, main product is **105**; b) Zn, I_2 [cat.], 130 °C, 3 h, 76% (reaction conditions optimised for compound **105**).

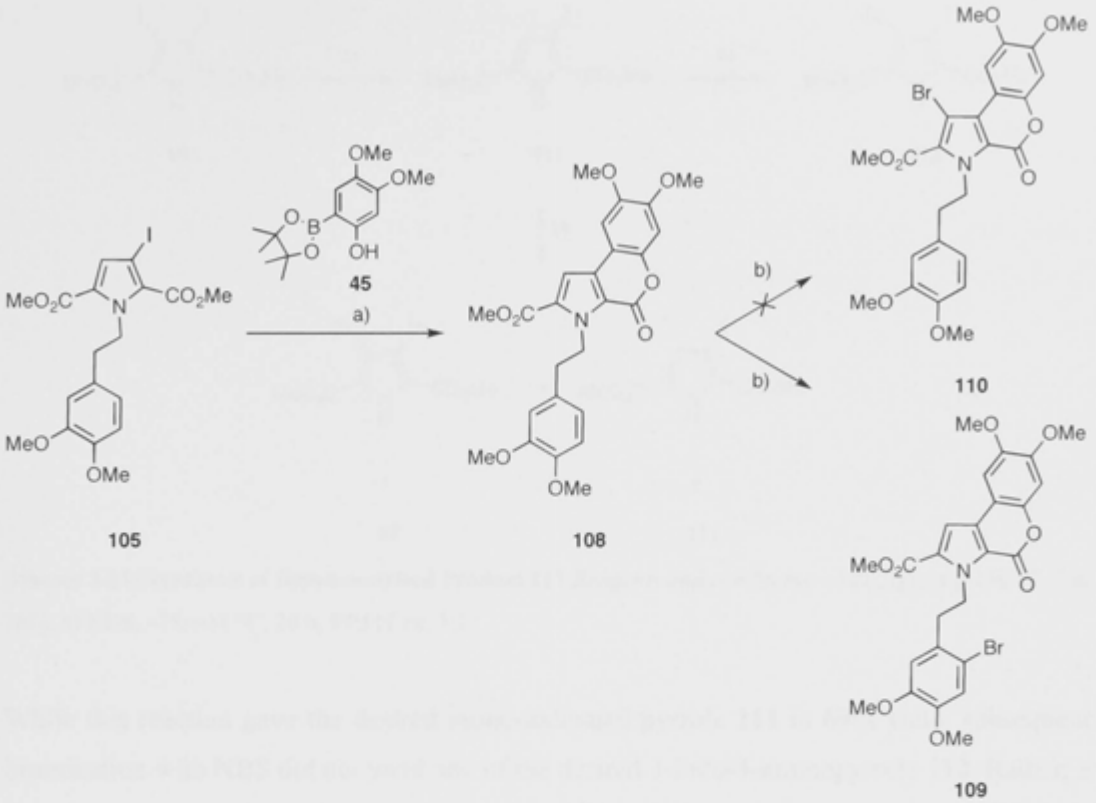
Although optimisation of the reaction conditions so as to secure a higher yield of a mono-cross-coupling product failed, the exclusive formation of mono-deiodinated pyrrole **105** represented a potentially useful outcome as this had finally resulted in an effective desymmetrisation of the molecule (Scheme 3.18). While such a desymmetrisation step employing zinc does not represent the most atom-economical approach it is, to the author's knowledge, the only effective method for the synthesis of the monohalogeno-derivatives of 2,5-dicarboxypyrroles.

Interestingly, attempted mono-halogenation of the 2,5-dicarboxypyrrole **106** with one equivalent of NBS or NIS to produce pyrrole **107** was unsuccessful, regardless of temperature employed (Scheme 3.19). Thus, this reaction resulted in a 1:1 mixture of starting material and the corresponding *bis*-halides **97** and **101**.



Scheme 3.19: Attempted Synthesis of a Mono-halogenated Pyrrole 107 from 106 *Reagents and conditions:* a) NIS or NBS, –78→18 °C.

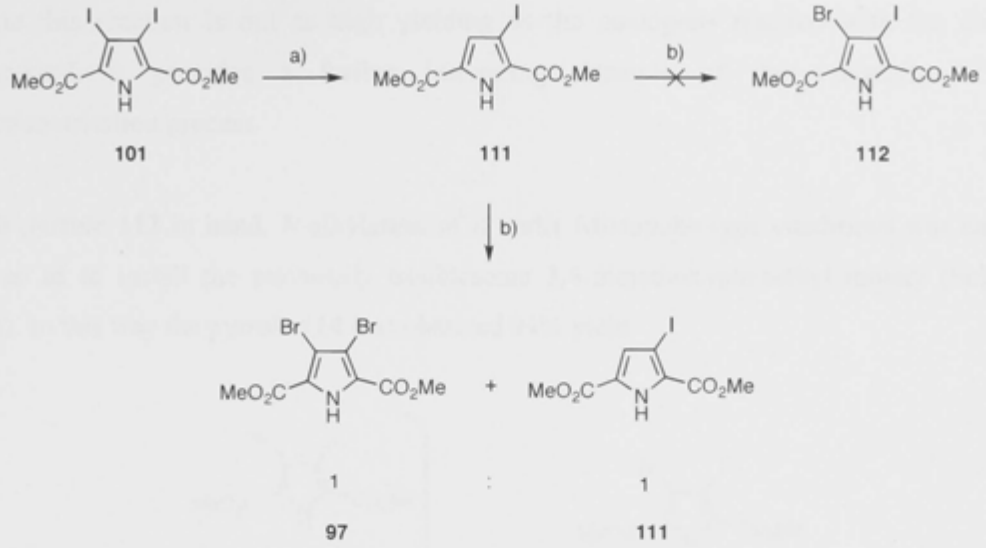
With pyrrole **105** in hand, it was expected that a cross-coupling reaction with compound **45** would, due to a decrease in steric hindrance, be more efficient when compared to the equivalent process involving congener pyrrole **102**. It was envisaged that after a successful cross-coupling reaction involving compound **105**, the product could be brominated or iodinated at the 4-position of the pyrrole and that a second cross-coupling reaction could then follow.



Scheme 3.20: Synthesis of Cross-coupled Product 108 and Subsequent Bromination *Reagents and conditions:* a) **45**, $Pd(PPh_3)_4$, K_2CO_3, 60 °C, 1 h, 85%; b) NBS, –78→18 °C, 20 h, 65%.

After optimisation, an overall yield of 85% was achieved for the cross-coupling reaction between monohalide **105** and boronic ester **45** which was carried out under microwave irradiation using conditions analogous to those defined by Suzuki and Miyaura.[15a] With the tetracyclic pyrrole **108** in hand, the synthesis of the eastern half of lamellarin G trimethyl ether had been completed (Scheme 3.20).

Disappointingly, after subjection of compound **108** to bromination with NBS the regioisomer, **109**, of the desired 4-bromopyrrole **110** was isolated as the major product of the reaction. Evidently the attached 3,4-dimethoxyaryl-moiety is a stronger nucleophile than the pyrrole ring with the ester- and the lactone-functional groups attached. Accordingly, it was necessary to return to the use of *bis*-iodide precursor **101** and perform a desymmetrisation with zinc (Scheme 3.21), an approach identified earlier as an efficient means for effecting the required mono-deiodination (Scheme 3.19).



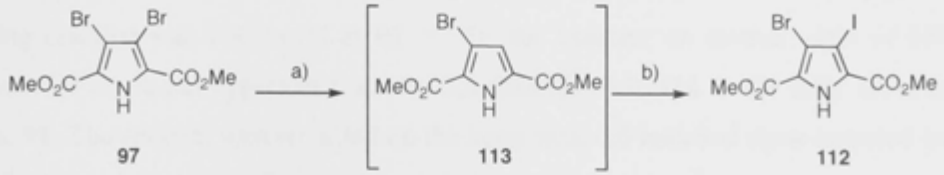
101 111 112

97 111

Scheme 3.21: Synthesis of Desymmetrised Product 111 *Reagents and conditions:* a) Zn, I_2 [cat.], 130 °C, 3 h, 76%; b) NBS, –78→18 °C, 20 h, **97**:**111** *ca.* 1:1.

While this reaction gave the desired mono-iodinated pyrrole **111** in 69% yield, subsequent bromination with NBS did not yield any of the desired 3-iodo-4-bromopyrrole **112**. Rather, a 1:1 mixture of starting material **111** and the previously obtained *bis*-bromide **97** was observed. An explanation for this may be that the initial bromination produces the desired 3-iodo-4-bromopyrrole **112** but this product is now more reactive towards further bromination (and in this case substitution of the iodide) than the starting material **111**.

As a result of the foregoing, the desymmetrisation of *bis*-bromide **97** (Scheme 3.22) was pursued. Best results for the formation of 3-iodo-4-bromopyrrole **112** were obtained in a one-pot approach. Thus, after conversion of the *bis*-bromopyrrole **97** into its mono-brominated analogue **113**, this was subjected to *in situ* iodination (with NIS) and thus delivering the desired 3-iodo-4-bromopyrrole **112** in 23% overall yield.

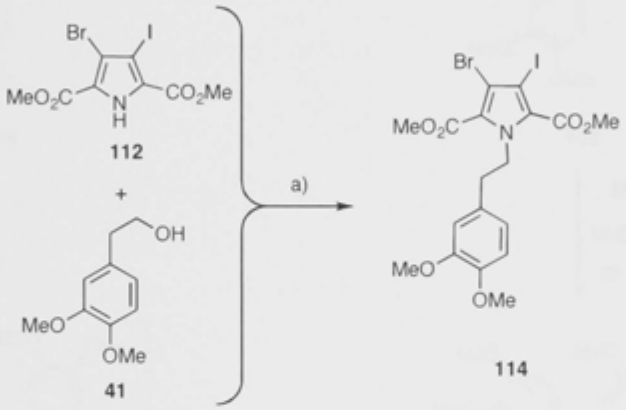


97 113 112

Scheme 3.22: Synthesis of 3-Iodo-4-bromopyrrole 112 *Reagents and conditions:* a) Zn, I_2 [cat.], 130 °C, 4 h; b) NIS, 18 °C, 16 h, 23% (over two steps).

While this reaction is not as high yielding as the analogous reaction with the diiodo-compound, it provides a further interesting example of the versatility of the desymmetrisation process.

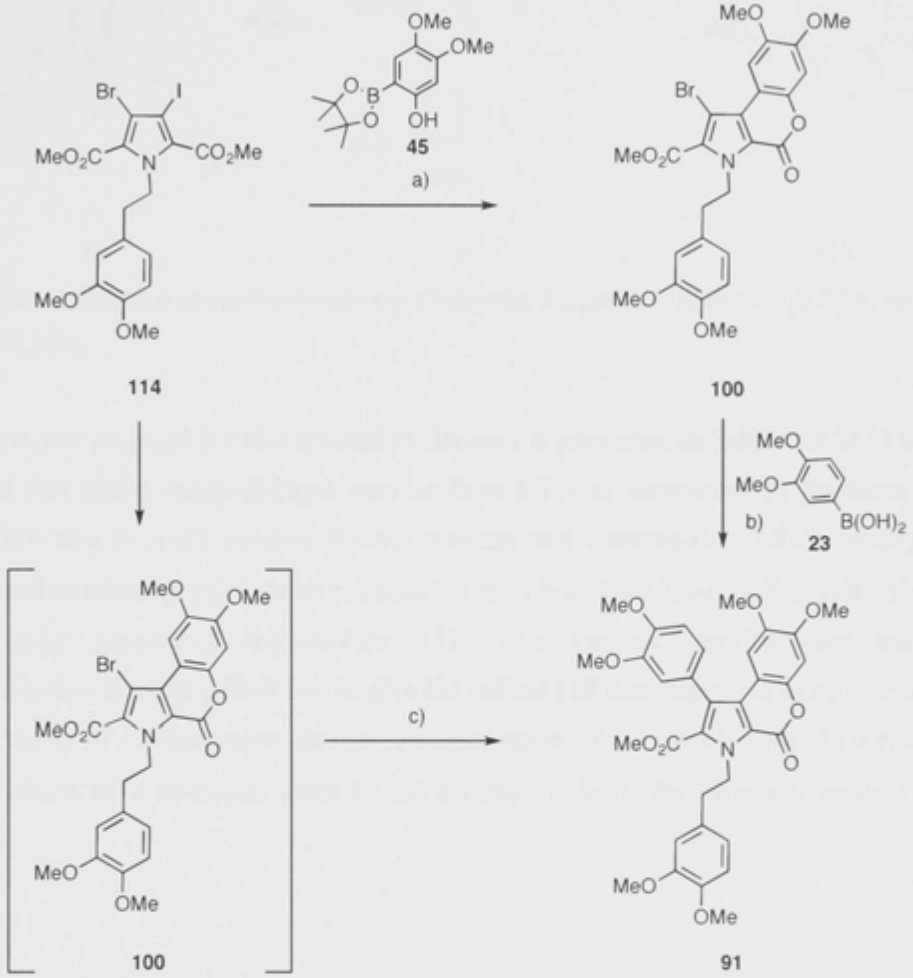
With pyrrole **112** in hand, *N*-alkylation of it under Mitsunobu-type conditions was carried out so as to install the previously troublesome 3,4-dimethoxyphenethyl moiety (Scheme 3.23). In this way the pyrrole **114** was obtained 94% yield.



Scheme 3.23: Synthesis of cross-coupling precursor 114 *Reagents and conditions:* a) DIAD, PPh_3, 18 °C, 4 h, 94%

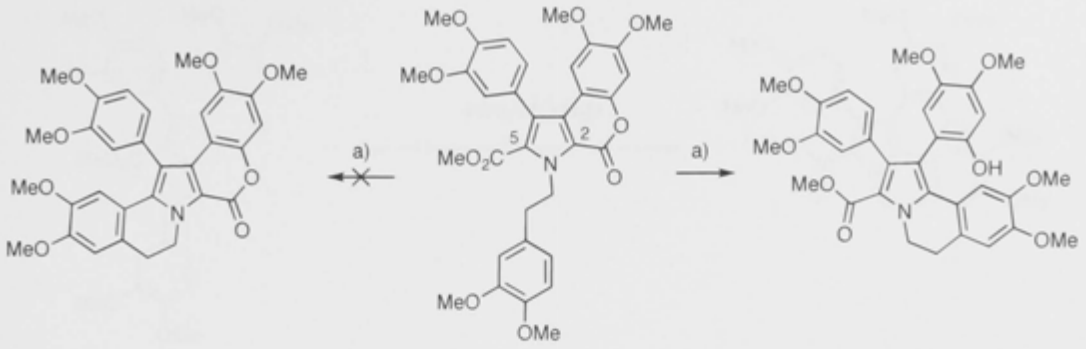
After optimisation, the cross-coupling reaction of substrates **114** and **45** produced compound **100** in 68% at 73% conversion (Scheme 3.24). The synthesis of key intermediate **91** was then completed by employing a second cross-coupling reaction of product **100** with commercially available boronic acid **23**. This reaction proceeded in excellent yield. Since both reactions were performed in the same reaction medium, it seemed sensible to develop a one-pot-procedure. In the event, the first coupling process was conducted at 80 °C with an excess of boronic ester **45** so as to achieve full conversion. Having accomplished that, 3,4-dimethoxyphenylboronic acid **23** was added to the reaction mixture and the second cross-coupling reaction was conducted at 95 °C. In this manner, an overall yield of 50% was achieved for a one-pot approach from the 3,4-dihalopyrrole **114** to the fully cross-coupled pyrrole **91**. The spectral data recorded on the latter material matched those reported by Iwao *et al.*[4] who had generated the same compound (through a significantly different approach) during the course of developing a total synthesis of lamellarin G trimethyl ether. The

acquisition of compound **91** therefore represents a formal synthesis of the natural product derivative **55**.



Scheme 3.24: Synthesis of Cross-coupled Product 91 *Reagents and conditions:* a) **45**, $Pd(PPh_3)_4$, K_2CO_3, 80 °C, 1 h, 68% (based on 73% conversion); b) **23**, $Pd(PPh_3)_4$, K_2CO_3, 90 °C, 1 h, 80%; c) **45**, $Pd(PPh_3)_4$, K_2CO_3, 80 °C, 1h, then **23**, 95 °C, 30 min, 50%.

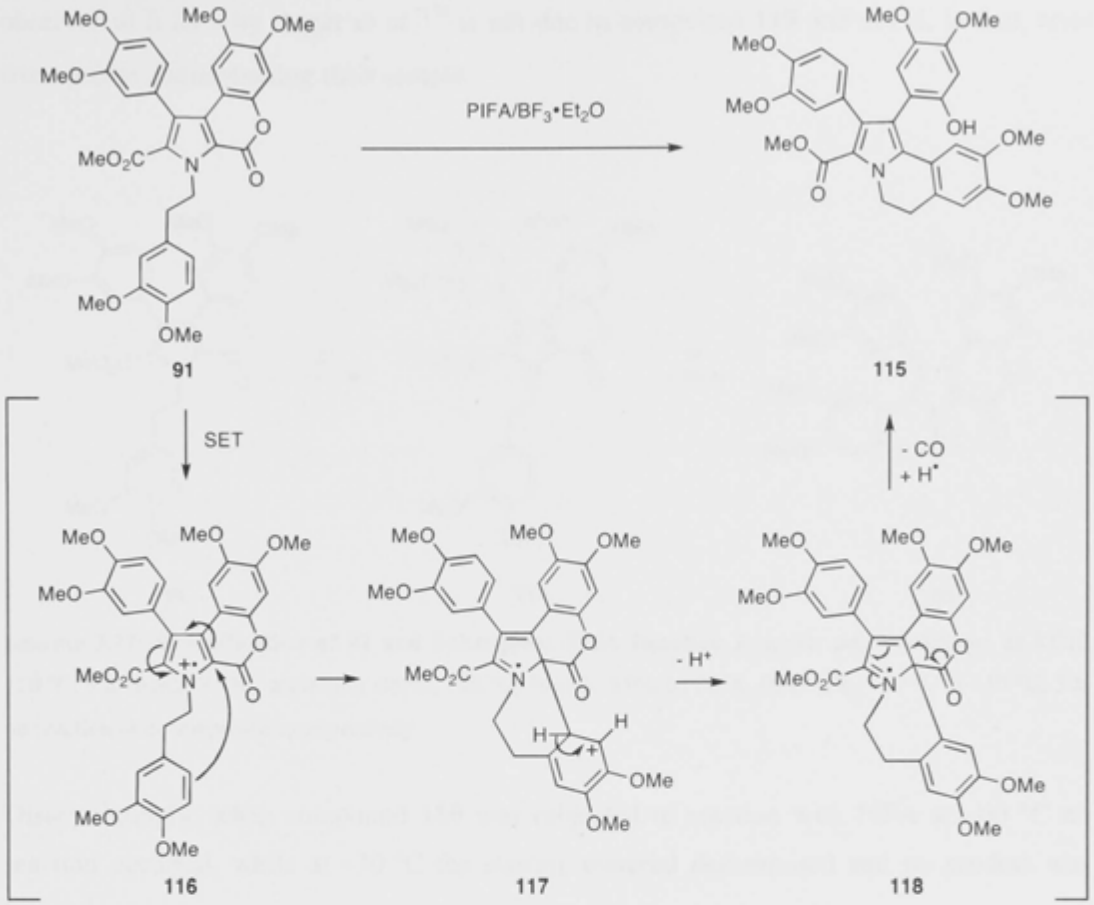
With pyrrole **91** in hand, the pivotal PIFA-oxidation reaction was pursued. Thus, when this compound was subjected to the reaction conditions used earlier (Scheme 3.25),[9] the hoped-for oxidation to form lamellarin G trimethyl ether did not occur. Rather, an oxidative ring-closure reaction occurred at the C2-position resulting in cleavage of the lactone moiety and thereby forming pyrrole **115** in 20% yield.



55 91 115

Scheme 3.25: Ring-closure Reaction occurred at C2-position *Reagents and conditions:* a) PIFA, $BF_3 \cdot OEt_2$, –40 °C, 3 h, 20%.

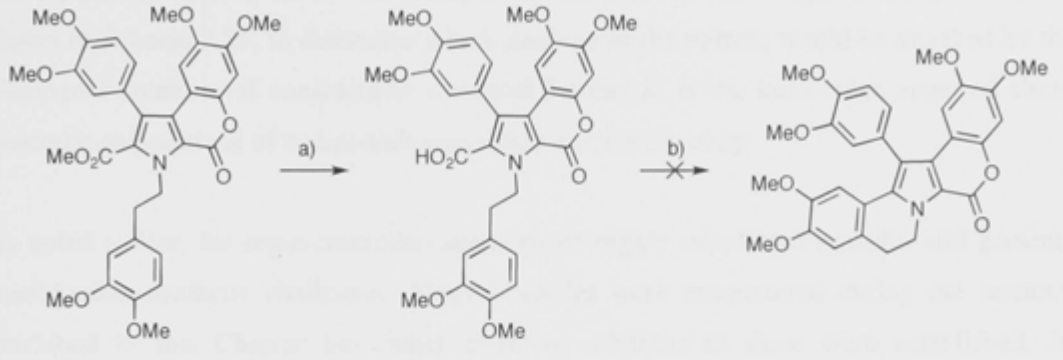
A mechanistic proposal for this unusual cyclisation is presented in Scheme 3.26. Thus, it is assumed that initial single-electron transfer from PIFA to compound **91** produces radical cation **116** that is itself attacked by the pendant and electron-rich 3,4-dimethoxyphenyl moiety and so forming a C-C-bond between the pyrrole and the 3,4-dimethoxyphenyl-moiety and thereby generating intermediate **117**. This cationic species then undergoes rearomatization through proton loss to give the radical **118** that fragments in a process driven by the release of carbon monoxide and rearomatization of the pyrrole ring. As a result, and after addition of a hydrogen atom to the phenoxy-radical, the observed product **115** is obtained.



Scheme 3.26: Mechanistic Proposal for the Conversion 91 → 115

In a prelude to an experiment designed to probe possible competition between cyclisation onto the C2- and C5-positions of pyrrole, ester **91** was saponified[1][4] using potassium hydroxide and, after acidic work-up, the corresponding *bis*-acid arising from cleavage of both the ester and lactone residues in the starting material **91** was obtained (Scheme 3.27). To reinstall the lactone ring and generate target compound **119**, it was necessary to treat this compound with catalytic quantities of *p*-toluenesulfonic acid (*p*-TsOH) monohydrate as well as 4 Å molecular sieves in refluxing toluene. By this method, compound **119** was obtained in 57% yield over the two steps involved. The ^{13}C NMR spectral data recorded on compound **119** matched those reported by Boger *et al.*[17] for this compound, except for a signal observed at δ 48.7 and the absence of one at δ 29.7. Since an HSQC-correlation experiment established that the signal observed at δ 48.7 is coupled to the two protons resonating at δ 5.03, the former resonance must be real. On this basis, the author believes that the signal

observed at δ 29.7 by Boger *et al.*[17] is not due to compound **119** and could, in fact, arise from grease contaminating their sample.



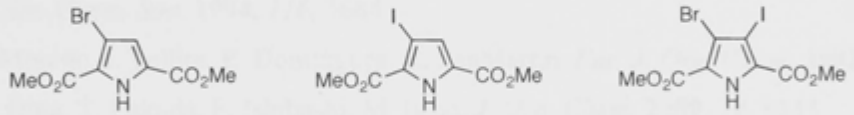
Scheme 3.27: Saponification of 91 and Subsequent PIFA Reaction *Reagents and conditions:* a) KOH, 150 °C, 3 h, then *p*-TsOH, molecular sieves, 110 °C, 30 min, 57%; b) PIFA, BF_3•OEt_2, –40 °C or –30 °C, 3 h, no reaction or decomposition, respectively.

Disappointingly, when compound **119** was subjected to reaction with PIFA at –40 °C no reaction occurred, while at –30 °C the starting material decomposed and no product was isolated.

3.4 Summary and Conclusions

An attempt to mimic key-bond-forming steps associated with the proposed biogenesis of the pentacyclic lamellarins failed. Nevertheless, the outcome of the competition experiment, as shown in Scheme 3.25, to determine which position of the pyrrole would be attacked by the *N*-tethered arene, is of considerable chemical interest as is the knowledge acquired about general manipulations of compounds containing a pyrrole moiety.

As noted earlier, the regio-controlled synthesis of highly substituted pyrroles still presents considerable synthetic challenges. Many obstacles were encountered during the research described in this Chapter but rather effective solutions to these were established. In particular, halogenation/reductive dehalogenation reaction sequences have been utilised to successfully desymmetrise various pyrroles and thereby providing the valuable new synthons shown in Figure 3.6. Furthermore, with the acquisition of 3-iodo-4-bromopyrrole **112**, a useful means of effecting regio-controlled Suzuki-Miyaura cross-coupling at those positions was established.



113 **111** **112**

Figure 3.6: Synthetically Valuable Halogen-containing Pyrroles Generated During the Course of Work Described in this Chapter

The application of these new protocols to the total synthesis of a previously inaccessible lamellarin is described in the following Chapter.

3.5 References

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4 *Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S*

4.1 Introduction to Lamellarin S 82

4.2 Modular Total Synthesis of Lamellarin G Trimethyl Ether 83

4.2.1 Retrosynthetic Analysis (Third Generation Approach) 85

4.2.2 Results and Discussion 86

4.2.3 Summary and Conclusion 89

4.3 Modular Total Synthesis of Lamellarin S 90

4.3.1 Retrosynthetic Analysis 90

4.3.2 Preparation of Building Blocks **125**, **126** and **127** Required for the Synthesis of Lamellarin S 91

4.3.3 Completion of the Total Synthesis of Lamellarin S 93

4.4 Summary and Conclusions 97

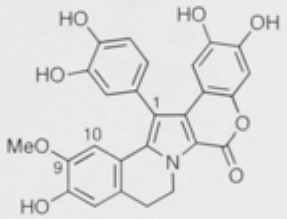
4.5 References 98

4 Modular Total Syntheses of Lamellarin G Trimethyl Ether and Lamellarin S

This Chapter details the development of modular total syntheses of lamellarin G trimethyl ether and lamellarin S. Since previous syntheses of lamellarin G trimethyl ether have been detailed in the preceeding Chapter the following Section is devoted to introducing the natural product lamellarin S.

4.1 Introduction to Lamellarin S

Lamellarin S (Figure 4.1) was isolated from an Australian tunicate *Didemnum sp.* collected at a depth of –15 meters near Durras, New South Wales in 1996 by Urban and Capon.[1]



120

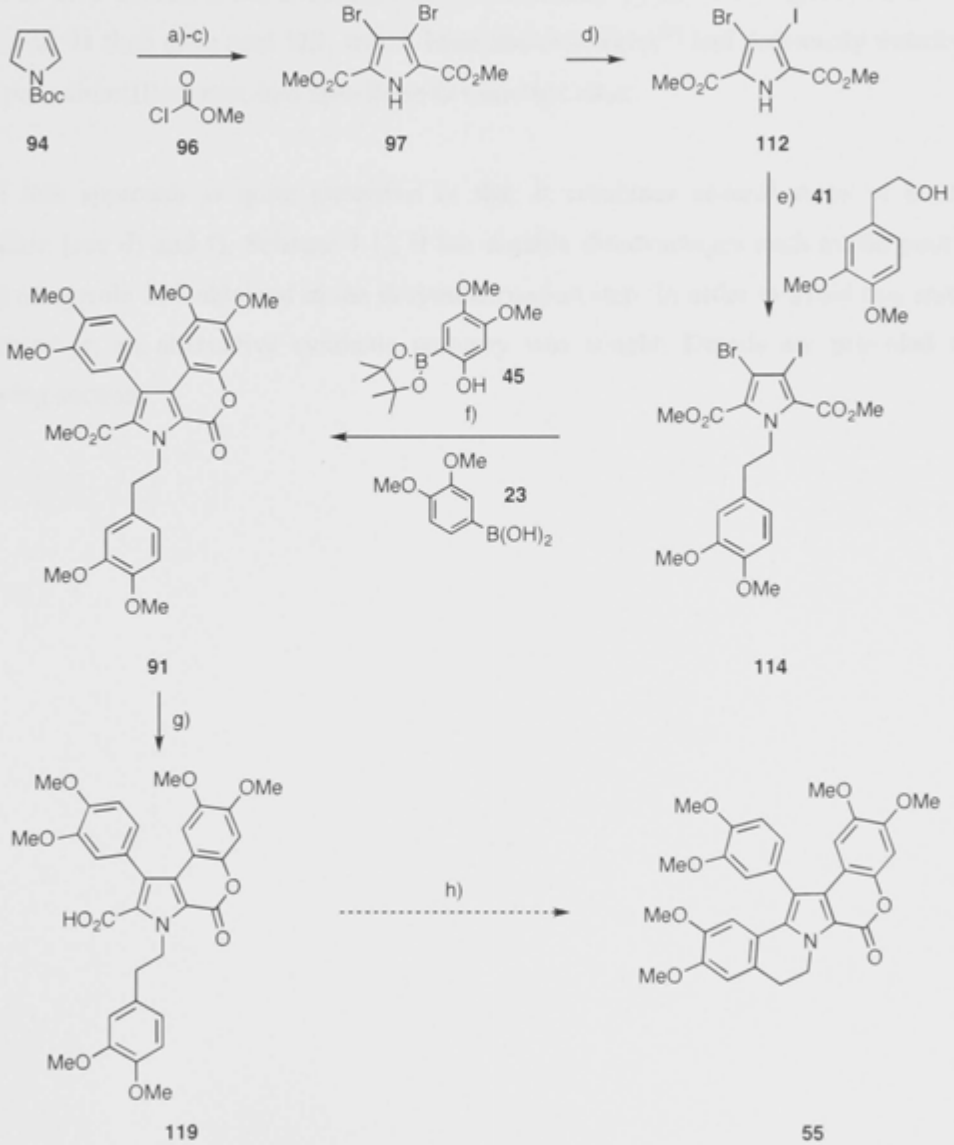
Figure 4.1: Structure of Lamellarin S

The illustrated structure of lamellarin S was elucidated using NMR and IR spectroscopic methods. In particular, INEPT techniques and a NOESY-experiment were used to assign the resonance due to H10 and established the proximity of the C9-methoxy group to this aromatic hydrogen.The C1-phenyl substituent is rotationally restricted and therefore capable of atropisomerism. Although, in principle, every member of the more complicated lamellarins can show atropisomeric effects, lamellarin S is the only natural product of this class that has been found to do. The optical rotation of this enantiomerically enriched material was measured repeatedly over a time period of 407 days after extraction and descended towards zero and thus implying racemisation was taking place.

No synthesis of lamellarin S has been reported to date.

4.2 Modular Total Synthesis of Lamellarin G Trimethyl Ether

In Chapter Three, a formal total synthesis of lamellarin G trimethyl ether (**55**) was described. The chosen synthetic pathway is shown again in Scheme 4.1.



Scheme 4.1: Formal Total Synthesis of Lamellarin G Trimethyl Ether as Described in Chapter 3
Reagents and Conditions: a) NBS, –78→18 °C, *ca.* 16 h, quantitative; b) *tert*-BuLi, then **96**, –78→18 °C, *ca.* 16 h, 58%; c) Br_2, 18 °C, 5 min, 99%; d) Zn, I_2 [cat.], 130 °C, 4 h, then NIS, 18 °C, 16 h, 23%; e) **41**, DIAD, PPh_3, 18 °C, 4 h, 94%; f) **45**, $Pd(PPh_3)_4$, K_2CO_3, 80 °C, 1 h, then **23**, 95 °C, 30 min, 50%; g) KOH, 150 °C, 3 h, then *p*-TsOH, molecular sieves, 110 °C, 30 min, 57%; h) $Pd(OAc)_2$, MeCN (see ref. [2]).

This synthesis of lamellarin G trimethyl ether commences with a three-step procedure reported by Fürstner *et al*,[3] who first reported the method for establishing the illustrated substitution pattern around pyrrole (compound **97**) starting from commercially available *tert*-butyl 1*H*-pyrrole-1-carboxylate (**94**). Reaction of compound **97** with zinc followed by *in situ* iodination with NIS produced the desymmetrised 3-iodo-4-bromopyrrole **112** that was subjected to a tandem cross-coupling reaction to furnish pyrrole **91**. Saponification of this compound **91** then gave acid **119**, which Iwao and coworkers[2] had previously transformed, using palladium(II)acetate, into lamellarin G trimethyl ether.

While this approach is quite attractive in that it combines several steps in a one-pot procedure [see d) and f), Scheme 4.1], it has notable disadvantages such as the poor yield (23%) of pyrrole **112** obtained in the desymmetrisation step. In order to avoid this and other shortcomings, an alternative synthetic pathway was sought. Details are provided in the following sections.

4.2.1 Retrosynthetic Analysis (Third Generation Approach)

In developing a new synthesis of lamellarin G trimethyl ether (**55**), *via* the pathway shown in Figure 4.2, a change in order of events (relative to the earlier approach summarised in Scheme 4.1) was expected to deliver the title product with greater efficiency. Thus, bromide **100** has been a part of the previously discussed second generation approach and was chosen as the first key target. It was envisaged that an alternative, higher-yielding approach to bromide **100** could be achieved by performing the Mitsunobu alkylation using pyrrole **121** which should be the product arising from bromination of compound **122**. Tricyclic pyrrole **122** should be accessible from the previously synthesised iodide **111** (see Section 3.3.2). The perceived advantages of this new approach are that it should avoid all previously encountered obstacles and that the iodide **111** is readily available in good yield.

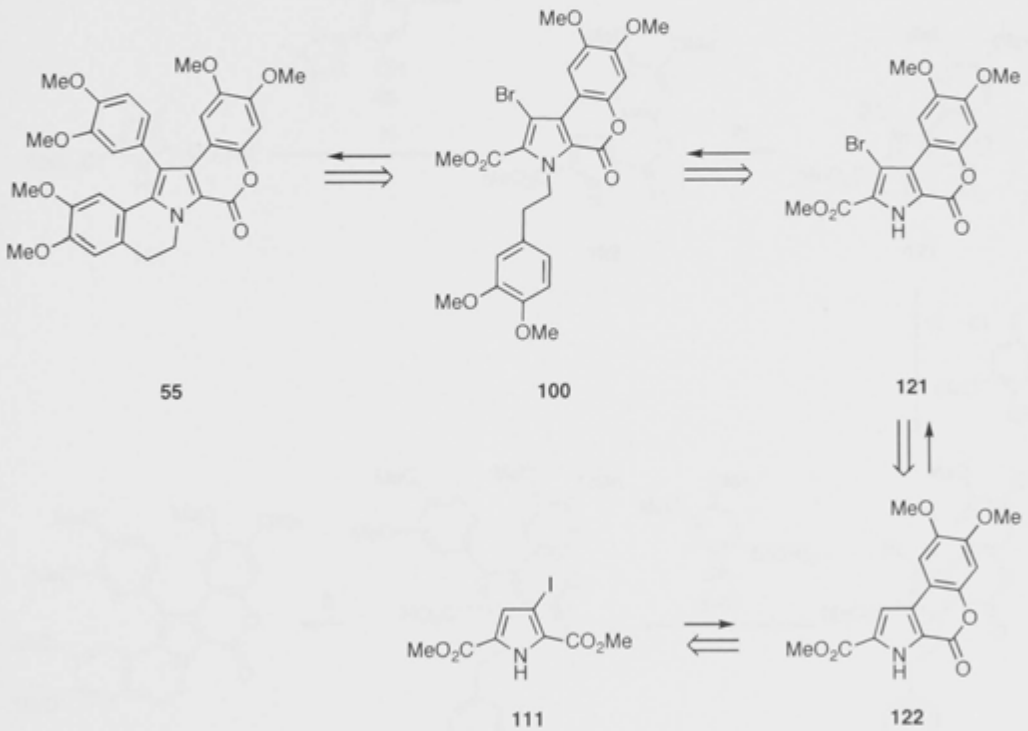
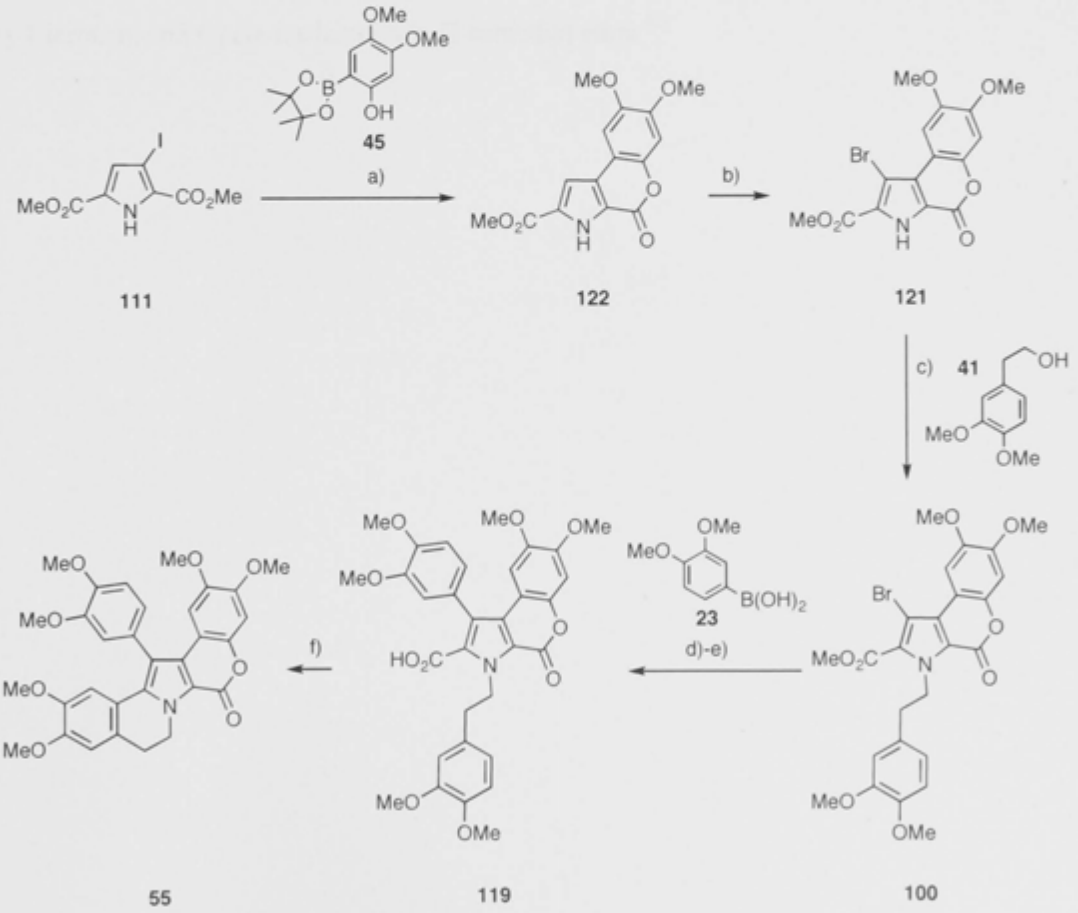


Figure 4.2: Retrosynthetic Analysis of Lamellarin G Trimethyl Ether Associated with Third Generation Approach

4.2.2 Results and Discussion

The introduction of the various aryl groups around the pyrrole core of target **55** was to be the first element of the new synthesis. Iodide **111** was, therefore, subjected to a Suzuki-Miyaura cross-coupling reaction[4] with boronate ester **45**, which conveniently introduced the desired lactone moiety as embodied in product **122**. This was obtained in 90% yield (Scheme 4.2). Further, selective bromination of compound **122** using NBS in DMF at 0-18 °C gave the mono-bromide **121** in 59% yield, which was then subjected to *N*-alkylation with β-phenethyl alcohol **41** using the Mitsunobu conditions[5] defined earlier (Scheme 3.23). The spectroscopic data obtained on product **100**, which was obtained in 62% yield, were in complete accord with the data obtained on the material obtained *via* the earlier route (Chapter 3).



Scheme 4.2: Synthesis of Lamellarin G Trimethyl Ether *Reagents and Conditions*: a) **45**, $Pd(PPh_3)_4$, K_2CO_3, 60 °C, 1 h, 90%; b) NBS, 0→18→50 °C, 16 h, 59%; c) **41**, DIAD, PPh_3, 18→50 °C, 15 h, 62%; d) **23**, $Pd(PPh_3)_4$, K_2CO_3, 90 °C, 1 h, 80%; e) KOH, 150 °C, 3 h, then *p*-TsOH, molecular sieves, 110 °C, 30 min, 57%; f) $Pd(OAc)_2$, MeCN, 82 °C, 14 h, 48%.

The installation of the final aromatic group associated with target **55** involved a Suzuki-Miyaura cross-coupling reaction of bromide **100** with commercially available aryl boronic acid **23**. This resulted in the generation of compound **91** in 80% yield (see Chapter 3). Saponification of the ester associated with compound **91** using a procedure detailed by Steglich[6] then gave the previously synthesised acid **119**.

The completion of the synthesis of target compound **55** involved treating precursor **119** with 1.1 equivalents of $Pd(OAc)_2$ in refluxing acetonitrile so as to effect the required decarboxylative Heck reaction. By such means target **55** was obtained in 48% yield as colourless crystals, the melting range of which (m.p. = 233-234 °C) was in good agreement with that recorded by Steglich *et al.*[6] (m.p. = 235 °C). Furthermore, as revealed in Table 4.1, the derived ^{1}H and ^{13}C NMR spectral data were in good agreement with those recorded by Liermann and Opatz for lamellarin G trimethyl ether.[7]

Table 4.1: Comparison of the ^{13}C and ^{1}H NMR Data Recorded on Samples of Synthetic Lamellarin G Trimethyl Ether (**55**) Derived from the Present Work and the Work of Liermann and Opatz [7]

^{13}C NMR Data (δ_C)		^{1}H NMR Data (δ_H)	
Compound **55** (this work) (200 MHz, $CDCl_3$)	Synthetic **55** (Liermann and Opatz) (100 MHz, $CDCl_3$)	Compound **55** (this work) (400 MHz, $CDCl_3$)	Synthetic **55** (Liermann and Opatz) (400 MHz, $CDCl_3$)
155.6 (C)	155.5 (C)	7.12 (dd, *J* 8.4 and 2.0 Hz, 1H)	7.11 (dd, *J* 8.1 and 1.8 Hz, 1H)
149.7 (C)	149.7 (C)	7.08 (d, *J* = 8.4 Hz, 1H)	7.07 (d, *J* = 8.1 Hz, 1H)
149.0 (C)	149.0 (C)	7.05 (d, *J* = 2.0 Hz, 1H)	7.05 (d, *J* = 1.8 Hz, 1H)
148.8 (C)	148.8 (C)	6.91 (s, 1H)	6.90 (s, 1H)
148.8 (C)	148.8 (C)	6.76 (s, 1H)	6.76 (s, 1H)
147.5 (C)	147.5 (C)	6.72 (s, 1H)	6.71 (s, 1H)
146.1 (C)	146.1 (C)	6.66 (s, 1H)	6.66 (s, 1H)
145.5 (C)	145.5 (C)	4.86-4.72 (m, 2H)	4.85-4.73 (m, 2H)
136.0 (C)	135.9 (C)	3.94 (s, 3H)	3.95 (s, 3H)
128.2 (C)	128.2 (C)	3.88 (s, 3H)	3.89 (s, 3H)
128.0 (C)	128.0 (C)	3.87 (s, 3H)	3.87 (s, 3H)
126.6 (C)	126.6 (C)	3.84 (s, 3H)	3.86 (s, 3H)
123.6 (CH)	123.6 (CH)	3.44 (s, 3H)	3.45 (s, 3H)
120.0 (C)	120.0 (C)	3.35 (s, 3H)	3.36 (s, 3H)
114.8 (C)	114.7 (C)	3.13 (t, *J* = 7.2 Hz, 2H)	3.12 (t, *J* = 6.8 Hz, 2H)
113.9 (CH)	114.0 (CH)		
113.8 (C)	113.7 (C)		
111.8 (CH)	111.9 (CH)		
111.0 (CH)	111.0 (CH)		
110.3 (C)	110.3 (C)		
108.6 (CH)	108.7 (CH)		
104.5 (CH)	104.5 (CH)		
100.5 (CH)	100.5 (CH)		
56.2 (CH_3)	56.2 (CH_3)		
56.2 (CH_3)	56.1 (CH_3)		
56.1 (CH_3)	56.0 (CH_3)		
56.1 (CH_3)	55.9 (CH_3)		
55.9 (CH_3)	55.5 (CH_3)		
55.5 (CH_3)	55.2 (CH_3)		
55.2 (CH_3)	55.2 (CH_3)		
42.4 (CH_2)	42.4 (CH_2)		
28.7 (CH_2)	28.7 (CH_2)		

4.2.3 Summary and Conclusion

A comparison of key features of the various total syntheses of lamellarin G trimethyl ether (**55**) reported so far is provided in Table 4.2 and this reveals that the one disclosed recently by Yadav is the shortest and most efficient. The present synthesis does not compare particularly favourably in terms of overall yield but, as revealed in the following section, its modular nature provides a pathway to a previously inaccessible member of the lamellarin family.

Table 4.2: *Comparison of Reported Syntheses of Lamellarin G Trimethyl Ether (55)*

Lead Author	Date Reported	# of Steps	Overall Yield	Ring-forming Sequence
Steglich	1997	four	32%	E+F → EF +A → EFAC → EFACD → EFACDB
Ruchirawat	2001	six	27%	ABF + E → ABFEC → ABFECD
Iwao	2003	seven	9%	A → AC + F →ACF + E → ACFED → ACFEDB
Handy	2004	eleven	9%	C + F → CF + A → CFA → CFAB + E → CFABED
Opatz	2008	eight	20%	AB + F → ABF + E → ABFEC → ABFECD
Gupton	2009	ten	7%	EF + A → EFAC → EFACD → EFACDB
Yadav	2009	four	45%	E + F → EF → EFD + AB → EFDABC
Present work	2010	eight	5%	C + E → CED + A → CEDA + F → CEDAF → CEDAFB

4.3 Modular Total Synthesis of Lamellarin S

The work described above served to establish the validity of a modular approach to the pentacyclic lamellarins. Accordingly, attention was turned to its use in the synthesis of lamellarin S (**120**), a target that incorporates five hydroxy groups and one methoxy group around its outer perimeter. As noted earlier, no synthesis of compound **120** had been reported prior to the one disclosed here.

4.3.1 Retrosynthetic Analysis

Earlier work in the Banwell group on the total synthesis of lamellarin K[8] demonstrated that isopropyl groups can serve as very effective protecting groups for the required free hydroxy units (Figure 4.3). Thus, by treating the pentacyclic pyrrole **123** with either $AlCl_3$ or BCl_3 the isopropyl ethers could, in the closing stages, be readily and selectively cleaved to liberate their respective phenols while leaving the corresponding methyl ether intact. Following a sequence analogous to that used for the synthesis of lamellarin G trimethyl ether (**55**), pyrrole **123** would be the product of a decarbonylative Heck-coupling reaction applied to acid **124**.

A necessary prelude to carrying out the synthesis of lamellarin S was the preparation of the two diisopropyl equivalents, **125** and **126**, of the dimethoxy-substituted aryl boronic ester **45** and acid **23**, as well as the preparation of the methoxyisopropyl equivalent, **127**, of alcohol **41**. Details of these preparations are provided in the following section.

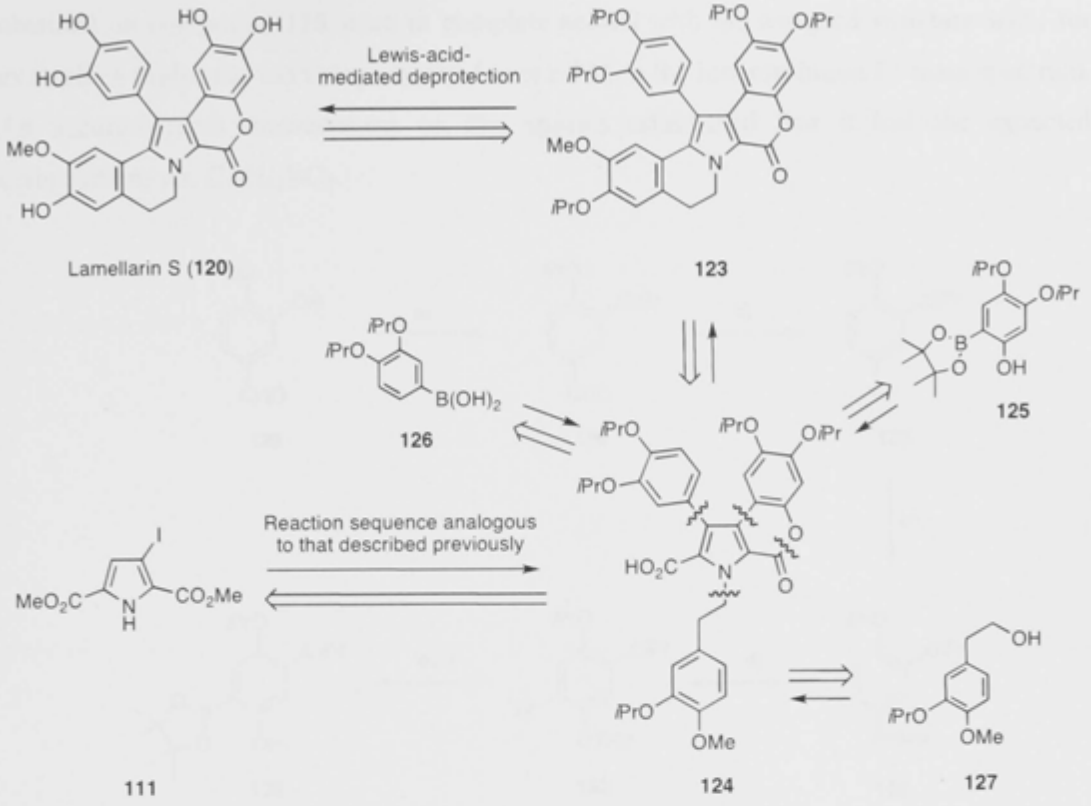
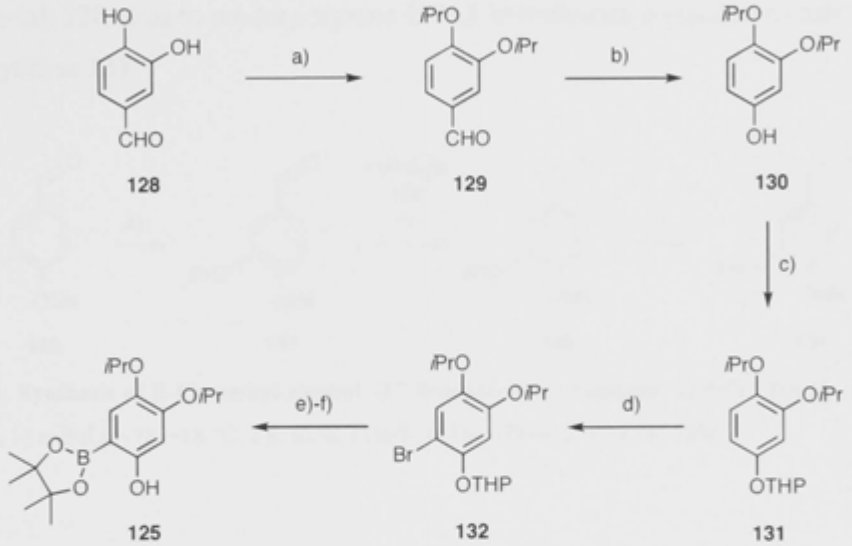


Figure 4.3: Retrosynthetic Analysis of Lamellarin S

4.3.2 Preparation of Building Blocks 125, 126 and 127 Required for the Synthesis of Lamellarin S

The reaction sequence used for the preparation of boronate ester **125** is shown in Scheme 4.3 and started with the conversion of commercially available 3,4-dihydroxybenzaldehyde (**128**) into the corresponding diisopropyl ether (**129**)[9] (89%) using isopropyl bromide in the presence of potassium carbonate. Treatment of the latter compound with hydrogen peroxide in the presence of sulfuric acid effected a Dakin oxidation and resulted in the formation of phenol **130**[9] (98%) that was converted into the corresponding tetrahydropyranyl (THP)-ether **131** (quant.) upon reaction with 3,4-dihydro-2*H*-pyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS). Reaction of arene **131** with 1.4 mole equivalents of NBS afforded the bromide **132** (86%) that was subjected to sequential treatment with *n*-butyllithium and triisopropylborate. Treatment of the material so formed with hydrochloric acid and pinacol resulted in cleavage of the THP-ether unit and a *trans*-esterification reaction at boron and thereby forming the target boronate ester **125** in 55% yield. The spectral data

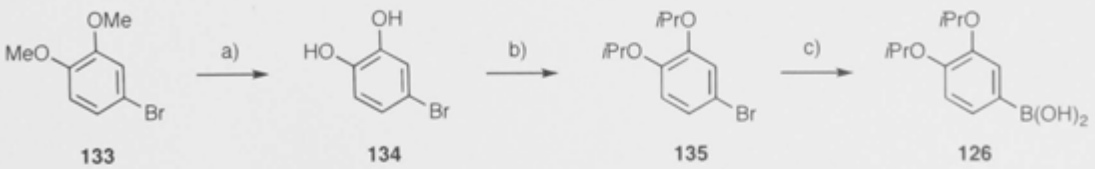
obtained on compound **125** were in complete accord with the assigned structure with, for example, a molecular ion being observed at *m/z* 336 in the low resolution EI mass spectrum. An accurate mass measurement on this species established that it had the expected composition, *viz*. $C_{18}H_{28}BO_5$.



128 129 130 131 132 125

Scheme 4.3: Synthesis of the Boronate Ester 125 *Reagents and Conditions*: a) *i*PrBr, K_2CO_3, 55 °C, 14 h, 89%; b) H_2O_2, H_2SO_4, 18 °C, 16 h, then NaOH, 18 °C, 30 min, 98%; c) DHP, PPTS, 18 °C, 2 h, 100%; d) NBS, Na_2CO_3, 0→18 °C, 3 h, 86%; e) B(O*i*Pr)$_3$, *n*-BuLi, –78→18 °C, 12 h, then HCl; f) pinacol, 18 °C, 24 h, 55% (over three steps).

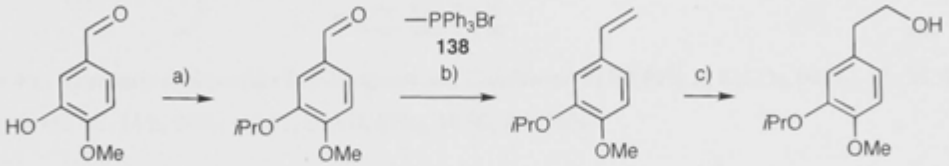
The boronic acid **126** was synthesised in a three-step sequence starting with BBr_3-mediated demethylation of 4-bromoveratrol (**133**) (Scheme 4.4).[10] The resulting catechol **134** was then subject to a two-fold isopropoxylation reaction so as to introduce the necessary isopropyl ether units. The material thus obtained (compound **135**) was subjected to sequential treatment with *n*-butyllithium and triisopropylborate followed by acidification with HCl and thus affording the previously unknown boronic acid **126**.



133 134 135 126

Scheme 4.4: Synthesis of Boronic Acid 126 *Reagents and Conditions*: a) BBr_3, –78→18 °C, 16 h, 73%; b) *i*PrBr, K_2CO_3, 55 °C, 14 h, 88%; c) B(O*i*Pr)$_3$, *n*-BuLi, –78→18 °C, 12 h, then HCl, 66%.

The other required synthon, β-phenethyl alcohol **127**, was prepared in three steps from commercially available isovanillin following procedures by Pampín (first two steps)[11] and Bach (last step).[12] Thus, isovanillin (**136**) was initially subjected to an isopropoxylation reaction to afford the aldehyde **137** (Scheme 4.5). This material was then treated with *n*-BuLi and Wittig-salt **138** so as to produce styrene **139**. A hydroboration reaction of that compound afforded synthon **127**.

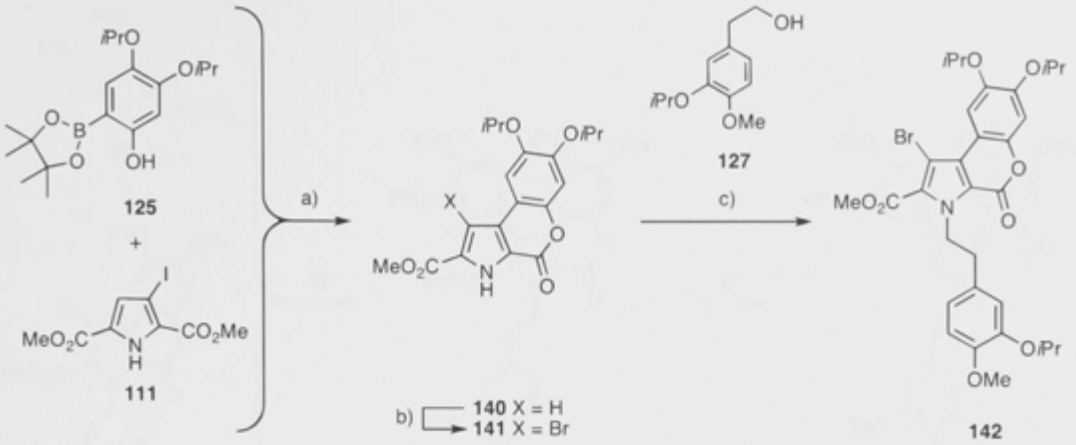


136 **137** **139** **127**

Scheme 4.5: Synthesis of β-Phenethyl alcohol 127 *Reagents and Conditions*: a) *i*PrBr, K_2CO_3, 55 °C, 14 h, quantitative; b) *n*-BuLi, –78→18 °C, 2 h, 82%; c) BH_3, H_2O_2, –78→18 °C, 14 h, 58%.

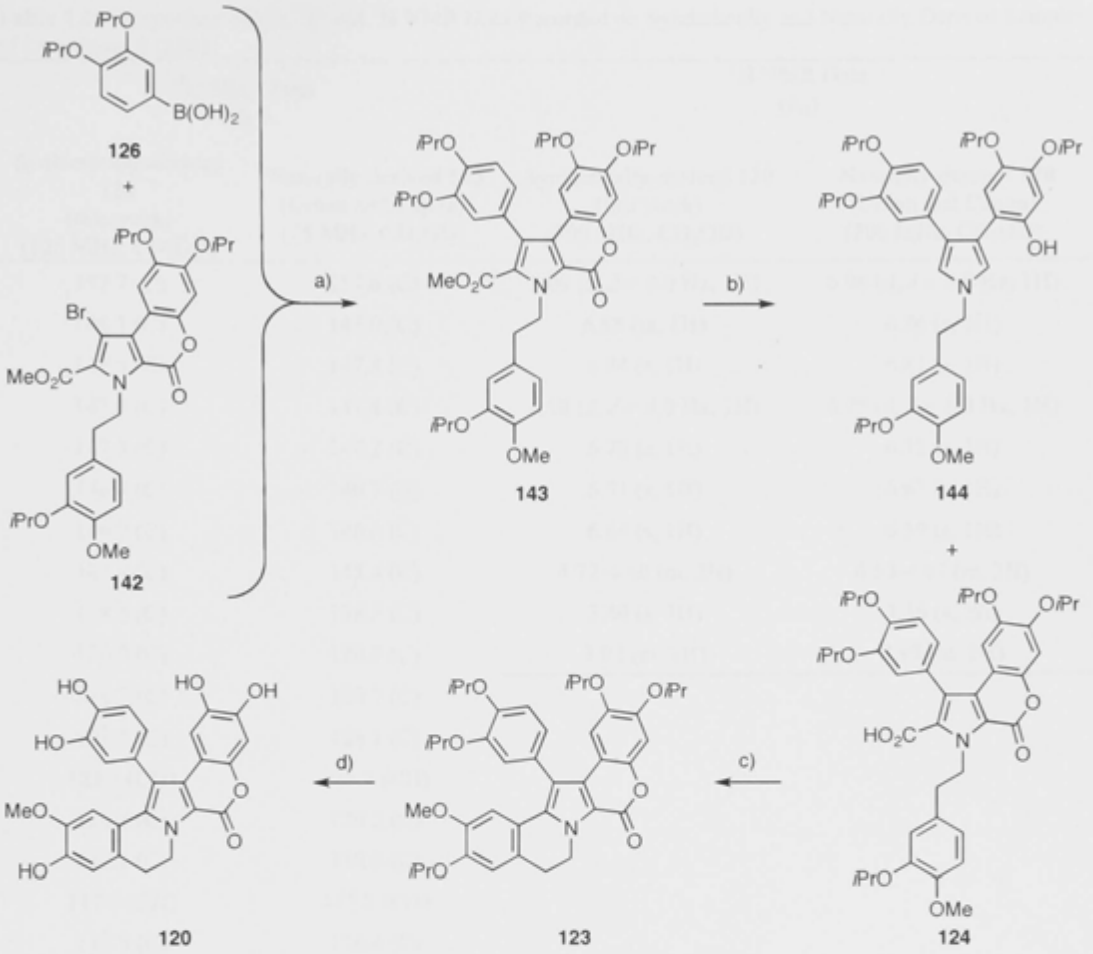
4.3.3 Completion of the Total Synthesis of Lamellarin S

Following the plan defined in the retrosynthetic analysis shown in Figure 4.2, the boronate ester **125** was subjected to a Suzuki-Miyaura cross-coupling reaction with pyrrole **111** and this resulted (Scheme 4.6) in the formation of the lactone **140** (92%). Bromination of this last compound with NBS followed by engagement of the product pyrrole **141** (94%) in a Mitsunobu reaction with the readily accessible β-phenethyl alcohol **127**[12] afforded the expected *N*-alkylation product **142** in 96% yield.



Scheme 4.6: Synthesis of Bromide 142 *Reagents and Conditions*: a) $Pd(PPh_3)_4$, K_2CO_3, 60 °C, 1 h, 92%; b) NBS, 0→18 °C, 14 h, 94%; c) **127**, DIAD, PPh_3, 18 °C, 1 h, 96%.

Cross-coupling of compound **142** with the aryl boronic acid **126** then gave pyrrole **143** in 67% yield (Scheme 4.7). Following the procedures used earlier (Scheme 4.2), the last compound was subjected to a saponification/re-lactonisation sequence but in addition to this producing the acid **124** (49%) required for the decarboxylative Heck reaction, the product **144** (16%) resulting from a two-fold decarboxylation was obtained. The reasons for the formation of this unwanted material may be the harsh conditions used for the saponification. Treatment of compound **124** with $Pd(OAc)_2$ in refluxing acetonitrile effected its conversion into the pentacyclic system **123** (56%) which represents the pentaisopropyl ether of lamellarin S. Finally, treatment of a dichloromethane solution of compound **123** with BCl_3 at –78 °C to 18 °C for *ca.* 3 h resulted in the cleavage of all five isopropyl aryl ether units and, therefore, the formation of lamellarin S (**120**) which was obtained as a pale-brown solid in 97% yield.



Scheme 4.7: Synthesis of Lamellarin S *Reagents and Conditions*: a) $Pd(PPh_3)_4$, K_2CO_3, 90 °C, 1 h, 67%; b) KOH, 130 °C, 4 h, then *p*-TsOH, molecular sieves, 110 °C, 30 min, 49% of **124**, 16% of **144**; c) $Pd(OAc)_2$, MeCN, 82 °C, 14 h, 56%; d) BCl_3, –78→18 °C, 3 h, 97%.

A comparison (Table 4.3) of the ^{13}C NMR spectral data derived from synthetic lamellarin S with those reported for the natural product, as reported by Urban and Capon,[1] reveal an excellent match. In particular, the chemical shifts of many of the signals are identical or differ by less than +0.1 ppm. The ^{1}H NMR spectral data also proved to be a good match, although in the spectrum derived from the synthetic material each of the tabulated signals had a small "mirror" peak that was always at slightly higher field. The precise origins of these remain unclear. Since analogous features are not apparent in the ^{1}H NMR spectrum of precursor **123** it seems unlikely that they are the result of conformational effects.

Table 4.3: Comparison of the ^{13}C and ^{1}H NMR Data Recorded on Synthetically and Naturally Derived Samples of Lamellarin S (**120**)

^{13}C NMR Data (δ_C)		^{1}H NMR Data (δ_H)	
Synthetically-derived **120** (this work) (125 MHz, CD_3OD)	Naturally-derived **120** (Urban and Capon) (75 MHz, CD_3OD)	Synthetically-derived **120** (this work) (500 MHz, CD_3OD)	Naturally-derived **120** (Urban and Capon) (300 MHz, CD_3OD)
157.7 (C)	157.6 (C)	7.00 (d, J = 8.0 Hz, 1H)	6.96 (d, J = 8.0 Hz, 1H)
148.1 (C)	148.0 (C)	6.88 (m, 1H)	6.86 (s, 1H)
147.5 (C)	147.4 (C)	6.84 (s, 1H)	6.81 (s, 1H)
147.4 (C)	147.4 (C)	6.78 (d, J = 8.0 Hz, 1H)	6.75 (d, J = 8.0 Hz, 1H)
147.3 (C)	147.2 (C)	6.76 (s, 1H)	6.72 (s, 1H)
146.8 (C)	146.7 (C)	6.71 (s, 1H)	6.67 (s, 1H)
146.7 (C)	146.6 (C)	6.64 (s, 1H)	6.59 (s, 1H)
143.4 (C)	143.4 (C)	4.72-4.60 (m, 2H)	4.53-4.67 (m, 2H)
138.6 (C)	138.5 (C)	3.40 (s, 3H)	3.36 (s, 3H)
130.0 (C)	129.9 (C)	3.02 (m, 2H)	2.97 (m, 2H)
128.7 (C)	128.7 (C)		
128.1 (C)	128.1 (C)		
123.7 (CH)	123.7 (CH)		
120.2 (C)	120.2 (C)		
119.1 (C)	119.0 (C)		
117.5 (CH)	117.5 (CH)		
116.5 (C)	116.4 (C)		
115.8 (CH)	115.8 (CH)		
113.8 (CH)	113.8 (CH)		
111.3 (C)	111.3 (C)		
110.4 (CH)	110.4 (CH)		
109.9 (CH)	109.8 (CH)		
104.2 (CH)	104.2 (CH)		
55.6 (CH_3)	55.6 (CH_3)		
43.6 (CH_2)	43.5 (CH_2)		
29.3 (CH_2)	29.3 (CH_2)		

An HPLC comparison of the synthetically derived sample of lamellarin S with an authentic sample of the natural product was kindly carried out by Professor Rob Capon and Dr Fabien Plisson (The University of Queensland). Co-elution of both compounds, analysed separately and as a mixture, established that the two materials were identical in terms of retention times and UV absorption spectra (the latter being acquired using a diode array detection system).

4.4 Summary and Conclusions

The assembly of lamellarin S by the means described above constitutes the first reported total synthesis of this natural product. The reaction sequence involves eleven steps and proceeds in an overall yield of *ca.* 6%. This is the final in a succession of total syntheses that have arisen out of a successful application of the protocols developed during the course of the research reported within this thesis.

Apart from the abovementioned total synthesis of lamellarin S, the developed methodologies have allowed for total syntheses of ningalin B and lamellarin G trimethyl ether. The considerable number of natural products made available through these new protocols is evidence of their effectiveness.

4.5 References

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5 Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapters 2 - 4

5.1 General Procedures ____ **100**

5.2 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 2 ____ **102**

5.3 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 3 ____ **119**

5.4 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 4 ____ **137**

5.5 References ____ **159**

5 Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapters 2 - 4

5.1 General Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 machine (operating at 300 MHz for proton and 75 MHz for carbon nuclei), a Varian MR400 instrument (operating at 400 MHz for proton and 100 MHz for carbon nuclei), a Varian VRX500 machine with an Inova console (operating at 500 MHz for proton and 125 MHz for carbon nuclei) or a Bruker AM-800 instrument (operating at 800 MHz for proton and 200 MHz for carbon nuclei). Chemical shifts were recorded as δ values in parts per million (ppm). Unless otherwise stated, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous sodium carbonate.

For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference and for those recorded in d_4-methanol, the "quintet" appearing at δ 3.35 was used as the internal reference. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral and assignment (where possible)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet; sept = heptet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ "triplet" was used to reference proton-decoupled ^{13}C NMR spectra. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Fourier Transform Infrared Spectrophotometer and samples were analyzed as thin films on KBr and NaCl plates (for liquids) or as a KBr disk (for solids).

Low-resolution ESI mass spectra were recorded in positive-ion mode on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a VG Fisions AUTOSPEC three-sector, double-focusing instrument.

Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected.

Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These

dips included a mixture of vanillin : sulfuric acid : ethanol (1 g : 1 g : 18 mL) or phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL). The retardation factor (R_f) values cited here have been rounded to the first decimal place.

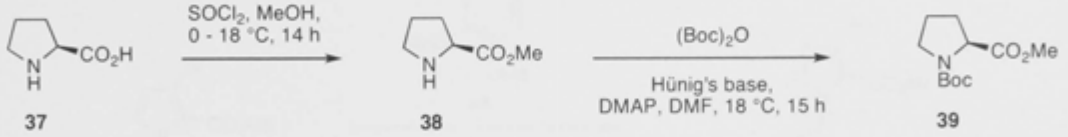
Flash chromatographic separations were carried out following protocols defined by Still *et al*[1] with silica gel 60 (40-63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated.

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, Boron Molecular, TCI, Strem or Lancaster Chemical Companies and were either used as supplied or, in the case of liquids, distilled when required.

Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, dichloromethane, acetonitrile and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[2] Spectroscopic grade solvents were used for all analyses.
Where necessary, reactions were performed under a nitrogen or argon atmosphere.

5.2 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 2

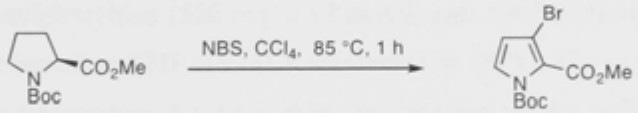
(*S*)-1-*tert*-Butyl 2-methyl pyrrolidine-1,2-dicarboxylate (39)



37 38 39

(*S*)-1-*tert*-Butyl 2-methyl pyrrolidine-1,2-dicarboxylate (**39**) was prepared from (*S*)-Proline (**37**) according to the method of Confalone *et al.*[3] and isolated in 88% yield and as a pale-yellow oil. The derived spectral data matched those reported in the literature.[3]

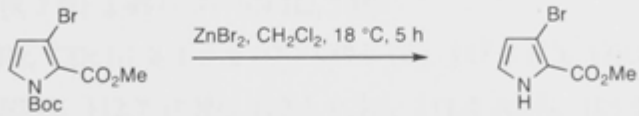
1-*tert*-Butyl 2-methyl 3-bromo-1*H*-pyrrole-1,2-dicarboxylate (40)



39 40

1-*tert*-Butyl 2-methyl 3-bromo-1*H*-pyrrole-1,2-dicarboxylate (**40**) was prepared from proline derivative **39** according to the method of Axford *et al.*[4] and isolated in 72% yield as a pale-yellow oil. The derived spectral data matched those reported in the literature.[4]

Methyl 3-bromo-1*H*-pyrrole-2-carboxylate (36)

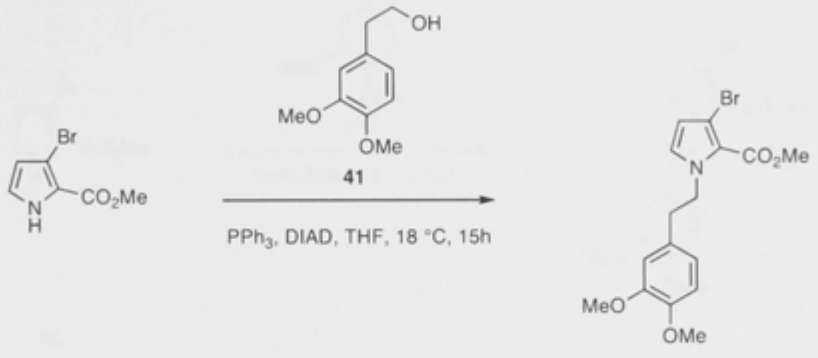


40 36

Methyl 3-bromo-1*H*-pyrrole-2-carboxylate (**36**) was prepared from pyrrole derivative **40** according to the method of Axford *et al.*[4] and isolated in 89% yield as a white, crystalline solid. The derived spectral data matched those reported in the literature.[4]

Methyl 3-bromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2-carboxylate (35)

Method A: **Via *Mitsunobu-Alkylation***



Diisopropyl azodicarboxylate (DIAD) (428 mg, 2.12 mmol) was added, dropwise, to a magnetically stirred solution of methyl 3-bromo-1*H*-pyrrole-2-carboxylate (**36**) (215 mg, 1.06 mmol), triphenylphosphine (556 mg, 2.12 mmol) and 3,4-dimethoxyphenethyl alcohol (**41**) (386 mg, 2.12 mmol) in THF (15 mL) maintained at 18 °C. The resulting solution was left stirring at this temperature for 15 h then concentrated, under reduced pressure, onto TLC-grade silica (1.5 g). The solid thus obtained was added to the top of a flash chromatography column that was then subjected to gradient elution (silica, CH_2Cl_2 → 9:1 v/v CH_2Cl_2/ethyl acetate gradient elution). Concentration of the appropriate fractions (R_f = 0.5) gave the *title carboxylate* ***35*** (291 mg, 75%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J = 8.1 Hz, 1 H), 6.63 (dd, J = 8.1 and 2.1 Hz, 1 H), 6.48-6.41 (complex m, 2 H), 6.14 (d, J = 3.0 Hz, 1 H), 4.45 (t, J = 6.9 Hz, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 2.93 (t, J = 6.9 Hz, 2 H).

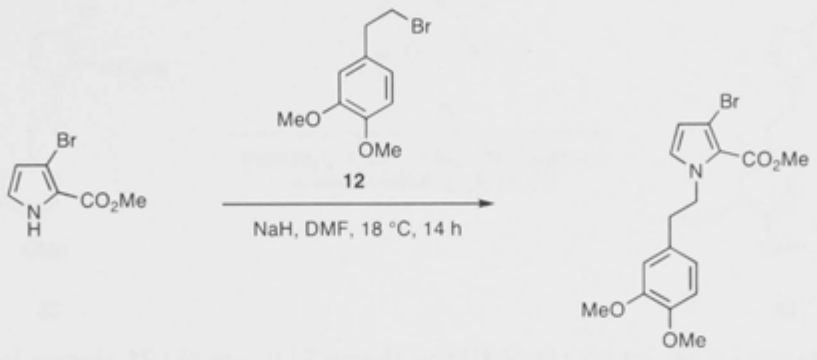
^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (C), 149.0 (C), 147.9 (C), 130.8 (C), 128.8 (CH), 121.0 (C), 119.6 (CH), 112.7 (CH), 112.1 (CH), 111.4 (CH), 105.5 (C), 56.1 (CH_3), 56.0 (CH_3), 53.0 (CH_3), 51.5 (CH_2), 37.9 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 3113, 2953, 2834, 1704, 1591, 1516, 1262, 1029, 806, 775, 633.

Mass Spectrum *m/z* (ESI) 407 [$(M+K)^+$, 5%], 392 [$(M+Na)^+$, 100], 390 [$(M+Na)^+$, 98], 336 (70).

HRMS Found: $(M+Na)^+$, 392.0291. $C_{16}H_{18}{}^{81}BrNO_4$ requires $(M+Na)^+$, 392.0305.

Method B:* Via *Base-induced Substitution Reaction

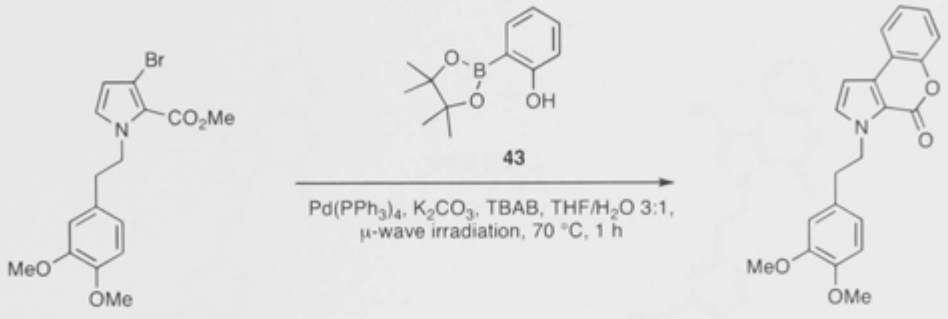


36 **35**

Sodium hydride (13 mg of a 60% dispersion in mineral oil, 0.33 mmol) was added to a magnetically stirred solution of pyrrole **36** (40 mg, 0.12 mmol) in DMF (1.5 mL) and the ensuing slurry was stirred at 18 °C for 0.5 h. After this time 3,4-dimethoxyphenethyl bromide (**12**) (152 mg, 0.60 mmol) was added to the reaction mixture that was then stirred for 14 h at 18 °C. The ensuing mixture was treated with water (20 mL) and then extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with water (2 × 5 mL) and brine (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_f = 0.2) furnished the *title compound **35*** (44 mg, 61%) as a clear, colourless oil.

This material was identical, in all respects, with an authentic sample of compound **35** obtained *via* the procedure described above.

3-(3,4-Dimethoxyphenethyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (42)



35 42

A solution of pyrrole **35** (45 mg, 0.12 mmol) in THF/H_2O (2.0 mL of 3:1 v/v mixture) was treated with potassium carbonate (85 mg, 0.62 mmol), TBAB (8 mg, 20 mol %) and boronic ester **43** (81 mg, 0.37 mmol). The resulting mixture was flushed with nitrogen then treated with $Pd(PPh_3)_4$ (7 mg, 5 mol %), flushed again with nitrogen then sealed and subjected to microwave irradiation at 70 °C for 1 h. The cooled reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_f = 0.2) furnished the *title compound* ***42*** (34 mg, 79%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1 and 1.5 Hz, 1 H), 7.43–7.24 (complex m, 3 H), 6.85 (d, *J* = 2.7 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 6.65 (dd, *J* = 8.1 and 2.1 Hz, 1 H), 6.57 (d, *J* = 1.8 Hz, 1 H), 6.54 (d, *J* = 2.7 Hz, 1 H), 4.57 (t, *J* = 6.9 Hz, 2 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.02 (t, J = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (C), 151.5 (C), 149.0 (C), 147.9 (C), 133.1 (CH), 130.8 (C), 130.6 (C), 128.0 (CH), 124.3 (CH), 123.1 (CH), 121.1 (CH), 118.3 (C), 117.3 (CH), 115.8 (C), 112.2 (CH), 111.4 (CH), 101.5 (CH), 56.1 (CH_3), 56.0 (CH_3), 51.2 (CH_2), 38.0 (CH_2).

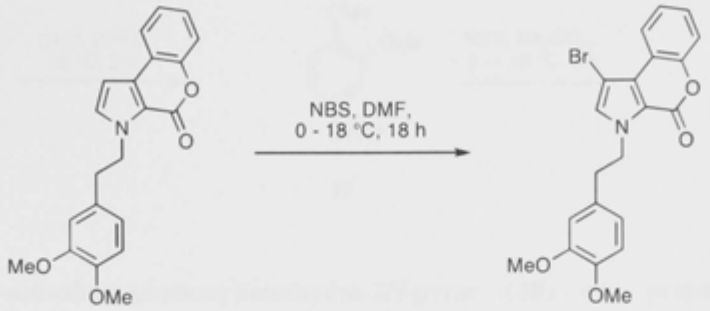
IR ν_{max} (NaCl)/cm^{-1} 3114, 2953, 1704, 1591, 1516, 1262, 1029, 807, 776, 633.

Mass Spectrum *m/z* (ESI) 388 [$(M+K)^+$, 5%], 372 [$(M+Na)^+$, 100], 350 [$(M+H)^+$, 95], 318 (10), 186 (10), 165 (15), 102 (11).

HRMS Found: $(M+Na)^+$, 372.1209. $C_{21}H_{19}NO_4$ requires $(M+Na)^+$, 372.1212.

Melting Point 120-139 °C.

1-Bromo-3-(3,4-dimethoxyphenethyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (44)



42 44

A magnetically stirred solution of pyrrole **42** (68 mg, 0.10 mmol) in DMF (2 mL) was cooled to 0 °C then treated, in one portion, with NBS (36 mg, 0.20 mmol) and the ensuing mixture was allowed to warm to 18 °C then stirred at this temperature for 18 h. The reaction mixture was then diluted with water (30 mL) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with water (1 × 40 mL) then brine (1 × 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:1 → 1:2 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fraction (R_f = 0.3 in 1:2 v/v pentane/diethyl ether) gave a crystalline solid. Recrystallisation (pentane/diethyl ether) of this material afforded the *title compound **44*** (62 mg, 74%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.1 Hz, 1 H), 7.40 (m, 2H), 7.30 (m, 1 H), 6.89 (s, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 8.1 and 1.8 Hz, 1 H), 6.58 (d, *J* = 1.8 Hz, 1 H), 4.61 (t, *J* = 6.9 Hz, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.05 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (C), 151.4 (C), 149.2 (C), 148.1 (C), 132.9 (CH), 130.1 (CH), 128.6 (C), 126.7 (CH), 124.3 (CH), 122.9 (C), 121.1 (CH), 117.6 (C), 117.4 (CH), 116.2 (C), 112.1 (CH), 111.5 (CH), 90.5 (C), 56.1 (CH_3), 56.0 (CH_3), 51.5 (CH_2), 37.9 (CH_2).

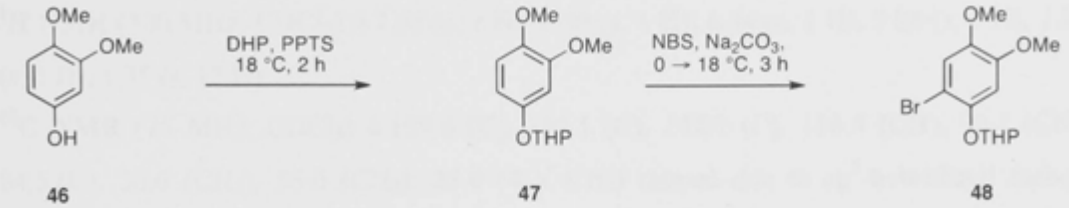
IR ν_{max} (NaCl)/cm^{-1} 3119, 2999, 2955, 2834, 1717, 1612, 1591, 1516, 1447, 1377, 1262, 1236, 1157, 1050, 1028, 964, 805, 751, 733.

Mass Spectrum *m/z* (EI, 70 eV) 431 and 429 ($M^{+\bullet}$, 26%), 164 (100), 151 (48).

HRMS Found: $M^{+\bullet}$, 427.0417. $C_{21}H_{18}{}^{79}BrNO_4$ requires $M^{+\bullet}$, 427.0419.

Melting Point 142-153 °C.

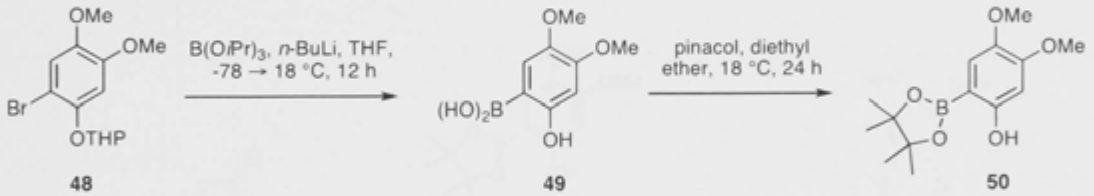
2-(2-Bromo-4,5-dimethoxyphenoxy)tetrahydro-2*H*-pyran (48)



46 47 48

2-(2-Bromo-4,5-dimethoxyphenoxy)tetrahydro-2*H*-pyran (**48**) was prepared from 3,4-dimethoxyphenol (**46**) according to the method of Handy *et al.*[5] and isolated in 83% yield and as a white, crystalline solid. The derived spectral data matched those reported in the literature.[5]

4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (45)



48 49 50

n-Butyllithium (1.6 M in hexane, 7.1 mL, 11.4 mmol) was added dropwise over 0.25 h to a magnetically stirred solution of compound (**48**) (2.79 g, 8.80 mmol) and triisopropyl borate (2.21 mL, 9.62 mmol) in THF (70 mL) at -78 °C and the reaction mixture was slowly allowed to warm up to 18 °C while stirring for 12 h. After the addition of HCl (20 mL of a 1 M aqueous solution) and stirring for another 0.5 h the phases were separated and the aqueous one was diluted with brine (20 mL) and extracted with THF (3 × 50 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow, mud-like solid (2.12 g). This solid was dissolved in diethyl ether (80 mL) then pinacol (1.78 g, 15.1 mmol) was added and the ensuing slurry was stirred magnetically for 24 h. Concentration of the resulting mixture under reduced pressure, subjection of the residue thus obtained to flash chromatography (silica, 1:1 ethyl acetate/hexane → ethyl acetate, gradient elution) and

concentration of the appropriate fractions (R_f = 0.6 in ethyl acetate) afforded the *title boronic ester* ***45*** (1.70 g, 69% over three steps) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 6.99 (s, 1 H), 6.44 (s, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 1.35 (s, 12 H).

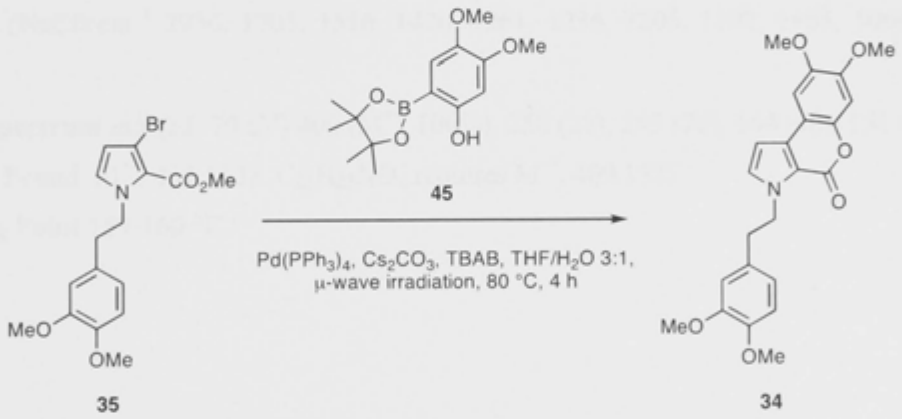
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (C), 154.1 (C), 142.7 (C), 116.4 (CH), 99.7 (CH), 84.5 (C), 56.6 (CH_3), 56.0 (CH_3), 25.0 (4 × CH_3) (signal due to sp^2-hybridized carbon bearing boron not observed).

IR ν_{max} (NaCl)/cm^{-1} 3447, 2978, 2936, 1622, 1511, 1459, 1414, 1387, 1300, 1250, 1237, 1211, 1158, 1140, 992, 859.

Mass Spectrum *m/z* (EI, 70 eV) 280 ($M^{+\bullet}$, 80%), 223 (42), 180 (100), 165 (55), 129 (78), 85 (55).

HRMS Found: $M^{+\bullet}$, 280.1483. $C_{14}H_{21}BO_5$ requires $M^{+\bullet}$, 280.1482.

3-(3,4-Dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (34)



A solution of pyrrole **35** (23 mg, 0.06 mmol), caesium carbonate (102 mg, 0.31 mmol), TBAB (4 mg, 0.01 mmol, 20 mol%), and boronic ester **45** (61 mg, 0.22 mmol) in THF/H_2O (0.5 mL of 4:1 v/v mixture) was placed in a glass reaction tube that was flushed with nitrogen. $Pd(PPh_3)_4$ (7 mg, 0.01 mmol, 10 mol%) was then added to the tube which was flushed with nitrogen once more then sealed and the resulting mixture subjected to microwave irradiation at 80 °C for 2 h. To effect full conversion, the cooled reaction mixture was treated with further aliquots of boronic ester **45**, caesium carbonate and $Pd(PPh_3)_4$ (same amounts as above). The resulting mixture was irradiated under the abovementioned

conditions for another 2 h then cooled, diluted with H_2O (30 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:1 v/v pentane diethyl ether → diethyl ether, gradient elution) and concentration of the appropriate fractions (R_f = 0.2 in 1:3 v/v pentane/diethyl ether) afforded a white solid. Recrystallisation of this material (pentane/diethyl ether) afforded the *title compound* ***34*** (11 mg, 43%) as white prisms.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1 H), 6.92 (s, 1 H), 6.82 (d, *J* = 2.7 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 6.63 (dd, *J* = 8.1 and 2.1 Hz, 1 H), 6.56 (d, *J* = 2.1 Hz, 1 H), 6.42 (d, *J* = 2.7 Hz, 1 H), 4.60 (t, *J* = 6.9 Hz, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.07 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C), 149.6 (C), 149.1 (C), 147.9 (C), 146.5 (C), 146.4 (C), 133.1 (CH), 131.4 (C), 130.7 (C), 121.1 (CH), 115.1 (C), 112.2 (CH), 111.4 (CH), 110.4 (C), 104.3 (CH), 100.9 (CH), 100.7 (CH), 56.6 (CH_3), 56.4 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 51.2 (CH_2), 38.0 (CH_2).

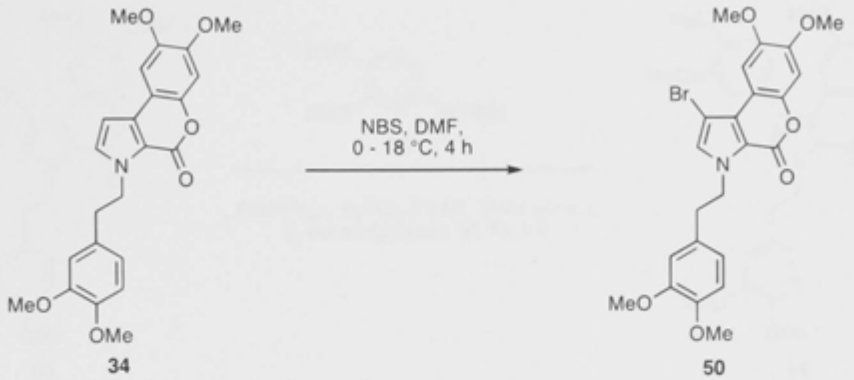
IR ν_{max} (NaCl)/cm^{-1} 2936, 1705, 1516, 1426, 1261, 1236, 1205, 1192, 1155, 1066, 1029, 1004.

Mass Spectrum *m/z* (EI, 70 eV) 409 ($M^{+\bullet}$, 100%), 258 (28), 245 (76), 164 (40), 151 (33).

HRMS Found: $M^{+\bullet}$, 409.1527. $C_{23}H_{23}NO_6$ requires $M^{+\bullet}$, 409.1525.

Melting Point 159-160 °C.

1-Bromo-3-(3,4-dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-*b*] -4(3*H*)-one (50)



N-Bromosuccinimide (12 mg, 0.07 mmol) was added, in one portion, to a magnetically stirred solution of compound **34** (13 mg, 0.03 mmol) in anhydrous DMF (0.3 mL) at 0 °C. The ensuing mixture was allowed to warm to 18 °C, stirred at this temperature for 4 h then diluted with H_2O (10 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with H_2O (1 × 30 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the resulting residue to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded the *title bromide* ***50*** (15 mg, 97%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 6.93 (s, 1 H), 6.89 (s, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.65 (dd, *J* = 8.1 and 1.5 Hz, 1 H), 6.59 (d, *J* = 1.5 Hz, 1 H), 4.61 (t, *J* = 6.9 Hz, 2 H), 3.98 (s, 3 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.06 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7 (C), 149.8 (C), 149.2 (C), 148.1 (C), 146.4 (C), 146.1 (C), 132.8 (CH), 130.2 (CH), 127.3 (C), 121.1 (CH), 115.3 (C), 112.1 (CH), 111.4 (CH), 109.7 (C), 104.0 (C), 100.7 (CH), 89.5 (C), 56.5 (CH_3), 56.4 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 51.5 (CH_2), 38.0 (CH_2).

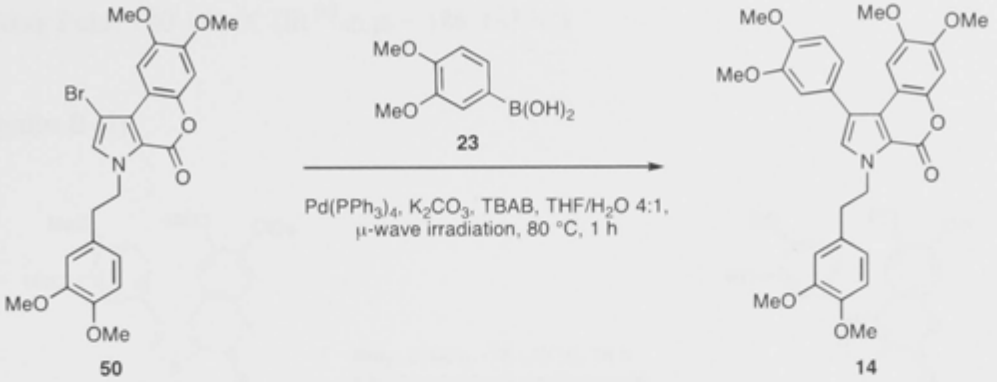
IR ν_{max} (NaCl)/cm^{-1} 2925, 1711, 1516, 1463, 1414, 1263, 1221, 1157, 1115, 1029, 1012, 966.

Mass Spectrum *m/z* (EI, 70 eV) 489 and 487 ($M^{+\bullet}$, 70 and 69%), 323 and 321 (73 and 74), 164 (100), 151 (95).

HRMS Found: $M^{+\bullet}$, 487.0639. $C_{23}H_{22}{}^{79}BrNO_6$ requires $M^{+\bullet}$, 487.0630.

Melting Point 142-144 °C.

Ningalin B Permethyl Ether (14)



A mixture of pyrrole **50** (26 mg, 0.05 mmol), boronic acid **23** (29 mg, 0.11 mmol), K_2CO_3 (37 mg, 0.19 mmol), TBAB (3 mg, 20 mol-%) and $Pd(PPh_3)_4$ (6 mg, 10 mol-%) in THF/water (0.65 mL of a 4:1 v/v mixture) was irradiated at 80 °C for 1 h in a microwave reactor. The cooled reaction mixture was diluted with water (20 mL) and ethyl acetate (20 mL) then the separated aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, dichloromethane → 9:1 v/v dichloromethane/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in 1:9 v/v dichloromethane/ethyl acetate) gave a white, crystalline solid. Recrystallisation (ethyl acetate/hexane) of this material afforded the *title compound* ***14*** (20 mg, 69%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 6.95-6.92 (m, 3 H), 6.88 (br s, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 6.74 (s, 1 H), 6.71 (dd, J = 8.2 and 1.8 Hz, 1 H), 6.58 (d, J = 1.8 Hz, 1 H), 4.65 (t, J = 7.0 Hz, 2 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.57 (s, 3 H), 3.11 (t, J = 7.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (C), 149.2 (C), 149.1 (C), 149.0 (C), 148.7 (C), 148.0 (C), 146.4 (C), 145.8 (C), 132.2 (C), 130.8 (C), 127.4 (C), 126.9 (C), 122.3 (C), 121.1 (CH), 119.3 (C), 115.1 (CH), 113.2 (CH), 112.2 (CH), 111.4 (CH), 111.2 (CH), 110.7 (CH), 104.9 (CH), 100.8 (CH), 56.4 (CH_3), 56.3 (CH_3), 56.1 (2 × CH_3), 56.1 (CH_3), 56.0 (CH_3), 51.3 (CH_2), 38.0 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 2927, 1709, 1515, 1464, 1415, 1259, 1244, 1174, 1139, 1027, 731.

Mass Spectrum *m/z* (EI, 70 eV) 545 ($M^{+\bullet}$, 100%), 394 (50), 381 (73).

HRMS Found: $M^{+\bullet}$, 545.2050. $C_{31}H_{31}NO_8$ requires $M^{+\bullet}$, 545.2050.

Melting Point 190-191 °C (lit.[6] m.p. = 186-187 °C).

Ningalin B (7)

Following the procedure detailed by Boger *et al.*,[6] a magnetically stirred solution of compound **14** (17 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) maintained under nitrogen was cooled to -78 °C then treated with BBr_3 (0.23 mL of a 2 M solution in hexane, 0.47 mmol) and the ensuing mixture then allowed to warm to 18 °C over 16 h. The reaction mixture was then diluted with methanol (1.5 mL) and concentrated under reduced pressure to give ningalin B (**7**) (14 mg, 96%) as an amorphous and dark-yellow solid.

^{1}H NMR (300 MHz, 79% $(CD_3)_2SO$/21% CD_3OD) δ 7.15 (s, 1 H), 7.05 (s, 1 H), 6.79 (d, J = 8.1 Hz, 1 H), 6.76 (d, J = 2.1 Hz, 1 H), 6.74 (s, 1 H), 6.63 (dd, J = 8.1 and 2.1 Hz, 1 H), 6.60 (d, J = 8.1 Hz, 1 H), 6.57 (d, J = 2.1 Hz, 1 H), 6.41 (dd, J = 8.1 and 1.5 Hz, 1 H), 4.47 (t, J = 7.2 Hz, 2 H), 3.11 (t, J = 7.2 Hz, 2 H).

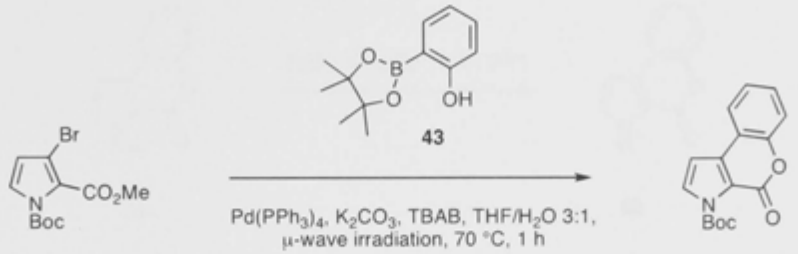
^{13}C NMR (75 MHz, 79% $(CD_3)_2SO$/21% CD_3OD) 155.2 (C), 146.4 (C), 145.6 (C), 145.5 (C), 145.4 (C), 145.1 (C), 144.2 (C), 142.5 (C), 133.1 (CH), 129.6 (C), 126.8 (C), 125.8 (C), 121.2 (CH), 120.1 (CH), 119.6 (CH), 117.4 (CH), 116.7 (C), 116.2 (CH), 116.0 (C), 114.4 (CH), 110.1 (C), 109.0 (CH), 103.9 (CH), 50.4 (CH_2), 37.6 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 2920, 1601.

Mass Spectrum *m/z* (ESI) 484 [$(M+Na)^+$, 16%], 462 [$(M+H)^+$, 85], 279 (100), 149 (20).

HRMS Found: $(M+H)^+$, 462.1182. $C_{25}H_{19}NO_8$ requires $(M+H)^+$, 462.1189.

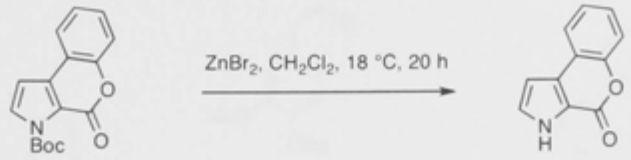
***tert*-Butyl 4-oxochromeno[3,4-*b*]pyrrole-3(4*H*)-carboxylate (51)**



A mixture of pyrrole **40** (70 mg, 0.23 mmol), potassium carbonate (160 mg, 1.16 mmol), TBAB (15 mg, 20 mol-%) 2-hydroxyphenylboronic acid, pinacol ester (**43**) (70 mg, 0.32 mmol), $Pd(PPh_3)_4$ (13 mg, 10 mol-%) in THF/water (4 mL of a 3:1 v/v mixture) was irradiated at 70 °C for 1 h in a microwave reactor. The cooled reaction mixture was then treated with Na_2CO_3 (10 mL of a saturated aqueous solution) and the ensuing mixture extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:1 v/v pentane/diethyl ether elution). Concentration of the appropriate fractions (R_f = 0.2) yielded a white solid. Recrystallisation (pentane/diethyl ether) of this material furnished the *title lactone* ***51*** (51 mg, 78%) as colourless prisms.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 3.3 Hz, 1 H), 7.78–7.71 (complex m, 1 H), 7.48-7.36 (complex m, 2 H), 7.34-7.24 (complex m, 1 H), 6.77 (d, *J* = 3.3 Hz, 1 H), 1.68 (s, 9 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 (C), 152.4 (C), 148.0 (C), 135.9 (C), 132.6 (CH), 129.8 (CH), 129.6 (CH), 124.3 (CH), 123.8 (C), 117.1 (CH), 116.8 (C), 104.7 (CH), 86.3 (C), 30.0 (3 × CH_3).
IR ν_{max} (NaCl)/cm^{-1} 2979, 2869, 1775, 1743, 1353, 1258, 1066, 754, 713.
Mass Spectrum *m/z* (ESI) 308 [$(M+Na)^+$, 77%], 286 [$(M+H)^+$, ~ 0.1], 252 (65), 230 (100).
HRMS Found: $(M+H)^+$, 286.1080. $C_{16}H_{15}NO_4$ requires $(M+H)^+$, 286.1079.
Melting Point 94-96 °C.

Chromeno[3,4-*b*]pyrrol-4(3*H*)-one (52)



51 52

Zinc bromide (250 mg, 1.11 mmol) was added to a magnetically stirred solution of lactone **51** (77 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) maintained under nitrogen. The ensuing mixture was stirred for 20 h at 18 °C and then treated with sodium hydrogen carbonate (20 mL of a saturated aqueous solution) and water (20 mL). The ensuing mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with water (1 × 50 mL) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution). Concentration of the appropriate fractions (R_f = 0.2) then furnished the *title compound* ***52*** (46 mg, 93%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (bs, 1 H), 7.82 (ddd, *J* = 7.8, 1.8 and 0.9 Hz, 1 H), 7.49-7.29 (complex m, 4 H), 6.78 (dd, *J* = 2.7 and 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2 (C), 151.5 (C), 130.3 (C), 129.2 (CH), 128.2 (C), 124.7 (CH), 123.6 (CH), 118.2 (CH), 117.6 (C), 117.3 (CH), 103.7 (CH).

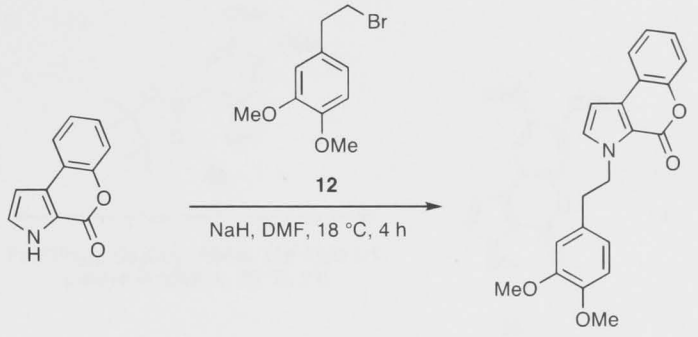
IR ν_{max} (NaCl)/cm^{-1} 3438, 3251, 2962, 1718, 1705, 1424, 11258, 1068, 786, 758, 724.

Mass Spectrum *m/z* (EI, 70 eV) 185 [($M^{+\bullet}$), 45%], 81 (50), 69 (100).

HRMS Found: $M^{+\bullet}$, 185.0479 $C_{11}H_7NO_2$ requires $M^{+\bullet}$, 185.0477.

Melting Point 191-193 °C.

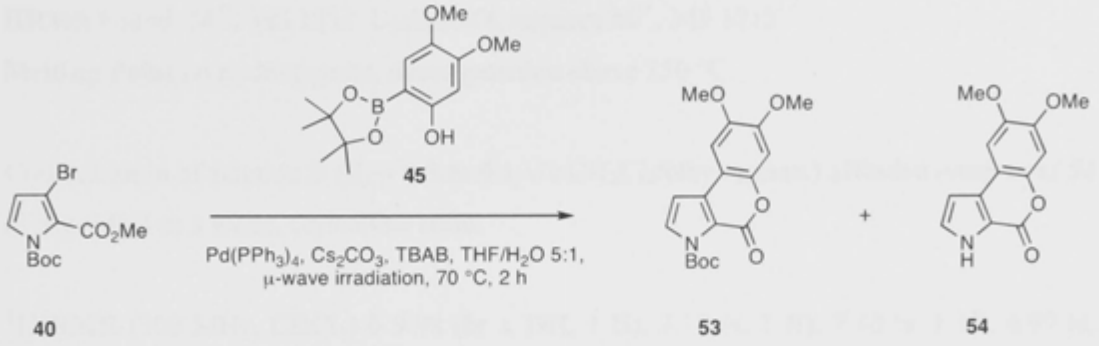
3-(3,4-Dimethoxyphenethyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (42)



Sodium hydride (16 mg of a 60% dispersion in mineral oil, 0.40 mmol) was added to a magnetically stirred solution of lactone **52** (46 mg, 0.25 mmol) in DMF (2 mL) and the ensuing slurry was stirred at 18 °C for 0.25 h. After this time 3,4-dimethoxyphenethyl bromide (**12**) (190 mg, 0.75 mmol) was added to the reaction mixture which was then stirred for 4 h at 18 °C. The ensuing mixture was treated with water (20 mL) and then extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with water (2 × 5 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_f = 0.2) furnished the *title compound* ***42*** (68 mg, 78%) as a white, crystalline solid.

This material was identical, in all respects, with an authentic sample of compound **42** obtained *via* the procedure described above.

***tert*-Butyl 7,8-dimethoxy-4-oxochromeno[3,4-*b*]pyrrole-3(4*H*)-carboxylate (53)**



A solution of pyrrole **40** (27 mg, 0.09 mmol) in THF/H_2O (0.6 mL of 5:1 v/v mixture) was treated with caesium carbonate (145 mg, 0.45 mmol), TBAB (6 mg, 0.02 mmol, 20 mol%) and boronate ester **45** (94 mg, 0.37 mmol). The resulting mixture was flushed with nitrogen then $Pd(PPh_3)_4$ (11 mg, 0.01 mmol, 11 mol%) was added and the reaction vessel again flushed with nitrogen before being sealed. The resulting mixture was subjected to microwave irradiation (150 W, 70 °C, 1 min ramp time) for 1 h then cooled and further portions of boronate ester **45** (80 mg, 0.29 mmol), caesium carbonate (128 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.01 mmol, 10 mol%) were added. The resulting mixture was, once again, irradiated under the abovementioned conditions for 1 h. The cooled reaction mixture was then diluted with H_2O (50 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, CH_2Cl_2 → 9:1 v/v CH_2Cl_2/ethyl acetate gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 9:1 v/v CH_2Cl_2/ethyl acetate) afforded the *title carboxylate* ***53*** (17 mg, 55%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 3.3 Hz, 1 H), 7.09 (s, 1 H), 6.90 (s, 1 H), 6.66 (d, J = 3.3 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 1.67 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 150.9 (C), 148.0 (C), 147.6 (C), 146.5 (C), 136.5 (C), 132.6 (CH), 115.8 (C), 108.8 (C), 104.5 (CH), 104.3 (CH), 100.5 (CH), 86.1 (C), 56.6 (CH_3), 56.5 (CH_3), 28.0 (3 × CH_3).

IR ν_{max} (NaCl)/cm^{-1} 1735, 1453, 1406, 1339, 1270, 1224, 1158, 995, 847.

Mass Spectrum *m/z* (EI, 70 eV) 345 [($M^{\bullet+}$), 10%,], 245 (90), 205 (88), 154 (100), 139 (75), 129 (57), 57 (62).

HRMS Found: $M^{+\bullet}$, 345.1212. $C_{18}H_{19}NO_6$ requires $M^{+\bullet}$, 345.1212.

Melting Point no melting point, decomposition above 250 °C.

Concentration of fraction B (R_f = 0.3 in 9:1 v/v CH_2Cl_2/ethyl acetate) afforded *compound* ***54*** (3 mg, 14%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (br s, NH, 1 H), 7.17 (s, 1 H), 7.10 (s, 1 H), 6.97 (s, 1 H), 6.68 (s, 1 H), 3.99 (s, 3 H), 3.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (C), 149.7 (C), 146.7 (C), 146.3 (C), 130.7 (C), 129.0 (CH), 116.5 (CH), 110.4 (CH), 104.6 (CH), 103.0 (CH), 101.1 (CH), 56.6 (CH_3), 56.4 (CH_3).

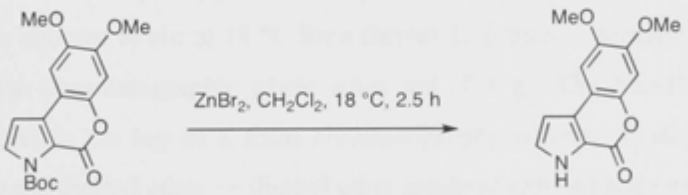
IR ν_{max} (NaCl)/cm^{-1} 3242, 2919, 1722, 1625, 1535, 1498, 1446, 1421, 1296, 1261, 1222, 1187, 1155, 1109, 1065, 1006, 772.

Mass Spectrum *m/z* (EI, 70 eV) 245 [($M^{\bullet+}$), 100%,], 230 (25), 129 (35), 85 (40), 69 (34).

HRMS Found: $M^{+\bullet}$, 245.0688. $C_{13}H_{11}NO_4$ requires $M^{+\bullet}$, 245.0688.

Melting Point no melting point, decomposition above 250 °C.

7,8-Dimethoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (54)

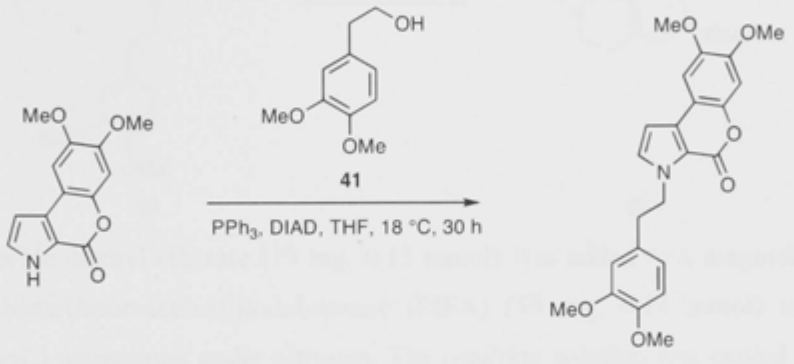


53 **54**

Zinc bromide (20 mg, 0.09 mmol) was added to a magnetically stirred solution of lactone **53** (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) maintained under nitrogen at 18 °C. After 2.5 h the reaction mixture was treated with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 3:1 v/v pentane/diethyl → diethyl ether → 1:1 diethyl ether/ethyl

acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in diethyl ether) afforded the *title compound* ***54*** (6 mg, 84%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample of compound **54** obtained *via* the procedure detailed immediately above.

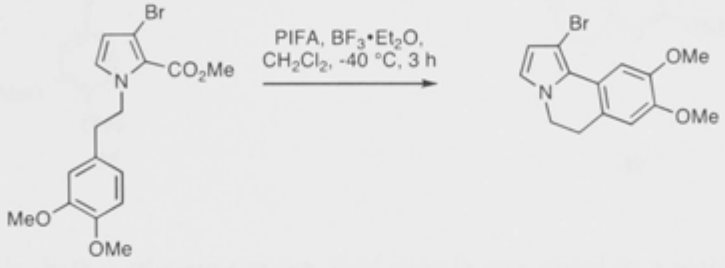
3-(3,4-Dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (34)



DIAD (22 mg, 0.11 mmol) was added, dropwise, to a magnetically stirred solution of compound **54** (18 mg, 0.07 mmol), triphenylphosphine (29 mg, 0.11 mmol) and alcohol **41** (20 mg, 0.11 mmol) in THF (1 mL) maintained at 18 °C. The resulting solution was left stirring at this temperature for 15 h then, so to ensure complete conversion, the same quantities of DIAD and triphenylphosphine specified above were added to the reaction mixture. This was allowed to stir at 18 °C for a further 15 h then concentrated under reduced pressure onto flash-chromatographic grade silica gel (0.4 g). The free-flowing solid thus obtained was added to the top of a flash chromatography column. Elution of the column (with 3:1 v/v pentane/diethyl ether → diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in diethyl ether) afforded the *title lactone* ***34*** (16 mg, 54%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample of compound **34** obtained *via* the procedure detailed above.

5.3 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 3

1-Bromo-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (85)



35 **85**

Boron trifluoride diethyl etherate (19 mg, 0.13 mmol) was added to a magnetically stirred solution of bis(trifluoroacetoxy)iodobenzene (PIFA) (59 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (25 mL) maintained under nitrogen. The resulting solution was cooled to 0 °C and then added to a magnetically stirred solution of pyrrole **35** (42 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (25 mL) maintained at –40 °C. The ensuing mixture was stirred at –40 °C for 3 h then treated with ammonia (4 mL of a 12% w/v aqueous solution) and water (10 mL) before being extracted into CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) and then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions ($R_f = 0.2$) afforded a solid that upon recrystallisation (pentane/diethyl ether) afforded the *title compound **85*** (10 mg, 29%) as clear, colourless crystals.

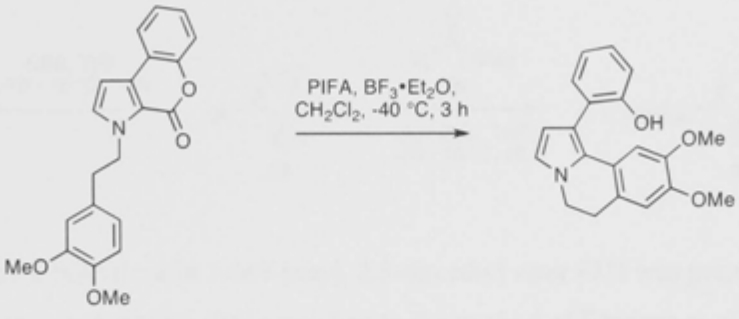
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.70 (s, 1 H), 6.60 (d, J = 2.7 Hz, 1 H), 6.23 (d, J = 2.7 Hz, 1 H), 4.00 (t, J = 6.3 Hz, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.97 (t, J = 6.3 Hz, 2 H).

Mass Spectrum *m/z* (ESI) 332 and 330 [$(M+Na)^+$, both 40%], 301 (50), 229 (60), 149 (60), 130 (61), 102 (100).

HRMS Found: $(M+Na)^+$, 330.0123. $C_{14}H_{14}{}^{79}BrNO_2$ requires $(M+Na)^+$, 330.0106.

The instability of this material precluded acquisition of any further spectroscopic and physical data.

2-(8,9-Dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)phenol (87)



42 87

Boron trifluoride diethyl etherate (49 mg, 0.35 mmol) was added to a magnetically stirred solution of bis(trifluoroacetoxy)iodobenzene (PIFA) (148 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (100 mL) maintained under a nitrogen atmosphere and the resulting solution was cooled to 0 °C. This solution was added, *via* cannula, to a magnetically stirred solution of pyrrole **42** (110 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (150 mL) maintained at –40 °C. The ensuing mixture was stirred at –40 °C for 3 h and then treated with ammonia (4 mL of a 12% w/v aqueous solution) and water (20 mL) before being extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (1 × 20 mL) and then dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution). Concentration of the appropriate fractions (R_f = 0.2) furnished the *title compound* ***87*** (9 mg, 9%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.15 (complex m, 2 H), 7.04-7.91 (complex m, 2 H), 6.77 (d, J = 2.7 Hz, 1 H), 6.68 (s, 1 H), 6.63 (s, 1 H), 6.21 (d, J = 2.7 Hz, 1 H), 5.51 (s, 1 H), 4.11 (t, J = 6.3 Hz, 2 H), 3.85 (s, 3 H), 3.38 (s, 3 H), 3.05 (t, J = 6.6 Hz, 2 H).

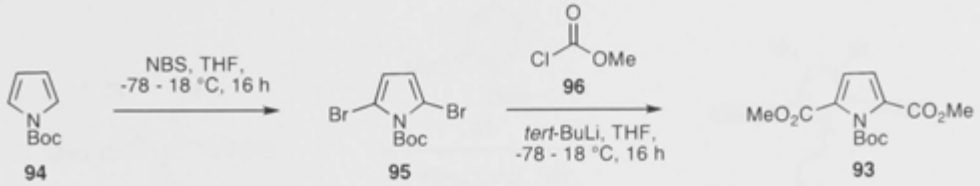
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 148.0 (C), 147.4 (C), 131.5 (CH), 129.1 (CH), 126.6 (C), 123.8 (CH), 122.0 (CH), 121.1 (CH), 120.6 (C), 115.1 (CH), 113.1 (CH), 111.1 (CH), 110.6 (CH), 106.8 (CH), 56.1 (CH_3), 55.4 (CH_3), 45.1 (CH_2), 29.6 (CH_2) (one signal obscured or overlapping).

IR ν_{max} (NaCl)/cm^{-1} 3436, 1643, 1330, 1285, 1251, 1208, 1138, 1029, 864, 795, 757, 731.

Mass Spectrum *m/z* (ESI) 344 [$(M+Na)^+$, 100%], 322 [$(M+H)^+$, 95].

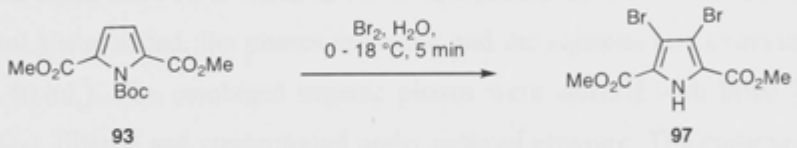
HRMS Found: $(M+Na)^+$, 344.1267. $C_{20}H_{19}NO_3$ requires $(M+Na)^+$, 344.1263.

Pyrrole-1,2,5-tricarboxylic acid 1-*tert*-butyl, 2,5-dimethyl ester (93)



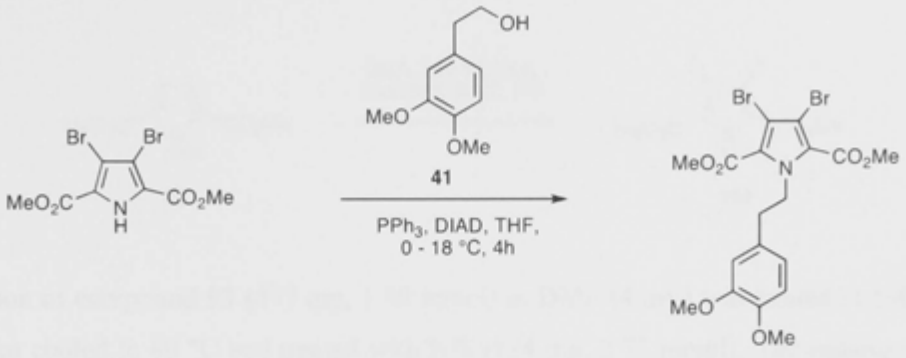
Pyrrole-1,2,5-tricarboxylic acid 1-*tert*-butyl, 2,5-dimethyl ester (**93**) was prepared from *tert*-butyl 1*H*-pyrrole-1-carboxylate (**94**) according to the method of Fürstner *et al.*[7] and isolated in 58% yield as a white, crystalline solid. The derived spectral data matched those reported.[7]

Dimethyl 3,4-dibromo-1*H*-pyrrole-2,5-dicarboxylate (97)



Pyrrole **97** was prepared in 99% yield from precursor **93** according to the method of Fürstner *et al.*[7] The derived spectral data matched those reported.[7]

Dimethyl 3,4-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2,5-dicarboxylate (98)



97 98

Dimethyl 3,4-dibromo-1*H*-pyrrole-2,5-dicarboxylate (**98**) (30 mg, 0.09 mmol) was dissolved in THF (2 mL) and treated with triphenylphosphine (28 mg, 0.11 mmol) and 3,4-dimethoxyphenethyl alcohol (**41**) (19 mg, 0.11 mmol) before being cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (22 mg, 0.11 mmol) was added dropwise and the ensuing mixture was allowed to warm to 18 °C and stirred for 4 h. Water (30 mL) and ethyl acetate (20 mL) was added, the phases separated and the aqueous one extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.4 in dichloromethane) afforded a white solid. Recrystallisation of this material (pentane/diethyl ether) afforded the *title compound* ***98*** (33 mg, 69%) as white prisms.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.1 Hz, 1 H), 6.67 (dd, *J* = 8.1 and 1.8 Hz, 1 H), 6.57 (d, *J* = 2.1 Hz, 1 H), 4.90 (t, *J* = 6.9 Hz, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.93 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (2 × C), 149.1 (C), 148.0 (C), 130.3 (C), 125.6 (2 × C), 121.3 (CH), 112.3 (CH), 111.4 (CH), 108.1 (2 × C), 56.2 (CH_3), 56.0 (CH_3), 52.2 (2 × CH_3), 50.1 (CH_2), 37.9 (CH_2).

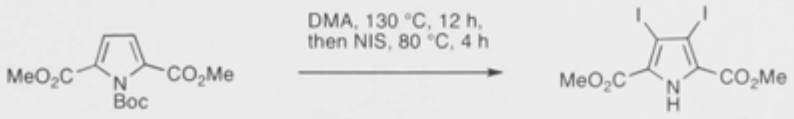
IR ν_{max} (NaCl)/cm^{-1} 2993, 2954, 2834, 1705, 1513, 1453, 1336, 1262, 1231, 856, 775.

Mass Spectrum *m/z* (EI, 70 eV) 505 ($M^{+\cdot}$, 24%), 164 (57), 151 (100).

HRMS Found: $M^{+\cdot}$, 502.9579. $C_{18}H_{19}{}^{79}Br_2NO_6$ requires 502.9575.

Melting Point 138-142 °C.

Dimethyl 3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (101)



93 **101**

A solution of compound **93** (477 mg, 1.68 mmol) in DMF (4 mL) was heated at 130 °C for 12 h then cooled to 80 °C and treated with NIS (834 mg, 3.71 mmol). The ensuing mixture was kept at 80 °C for 4 h then cooled and concentrated to dryness (50 °C under high vacuum). The byproduct of the reaction, succinimide, was removed by sublimation at 60 °C under high vacuum for 24 h. The resulting light-brown solid was recrystallised (dichloromethane/pentane) to give the *title compound* ***101*** (707 mg, 97%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (broad s, 1 H), 3.95 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (2 × C), 127.6 (2 × C), 85.7 (2 × C), 52.7 (2 × CH_3).

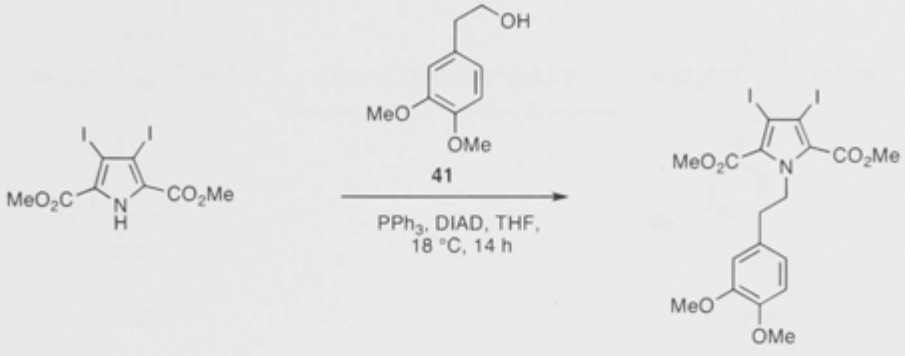
IR ν_{max} (KBr)/ cm^{-1} 3379, 2951, 1708, 1510, 1432, 1264, 1033, 943, 799, 776, 624.

Mass Spectrum *m/z* (EI, 70 eV) 435 ($M^{+\cdot}$, 100%), 403 (26), 372 (40), 345 (24).

HRMS Found: $M^{+\cdot}$, 434.8467. $C_8H_7{}^{127}I_2NO_4$ requires $M^{+\cdot}$, 434.8465.

Melting Point no melting point, decomposition above 240 °C.

Dimethyl 1-(3,4-dimethoxyphenethyl)-3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (102)



101 102

Dimethyl 3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (**101**) (0.653 g, 1.50 mmol) was dissolved in THF (50 mL) and the resulting solution treated with triphenylphosphine (0.473 g, 1.80 mmol) and 3,4-dimethoxyphenethyl alcohol (**41**) (0.33 g, 1.80 mmol) before being cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (0.36 g, 1.80 mmol) was added dropwise over 3 min. and the ensuing mixture was allowed to warm to 18 °C and stirred at this temperature for 4 h. The reaction mixture was concentrated on silica (2.0 g) and the solid thus obtained subjected to flash chromatography (silica, dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.2) furnished the *title compound* ***102*** (0.791 g, 88%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 8.1 and 1.8 Hz, 1 H), 6.53 (d, *J* = 1.5 Hz, 1 H), 4.89 (t, *J* = 6.9 Hz, 2 H), 3.85 (s, 9 H), 3.83 (s, 3 H), 2.93 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 (2 × C), 149.1 (C), 148.0 (C), 130.4 (C), 130.3 (2 × C), 121.3 (CH), 112.2 (CH), 111.4 (CH), 86.1 (2 × C), 56.2 (CH_3), 56.1 (CH_3), 52.1 (2 × CH_3), 50.7 (CH_2), 38.0 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 2950, 1721, 1515, 1261, 1237, 1157, 1028, 1262.

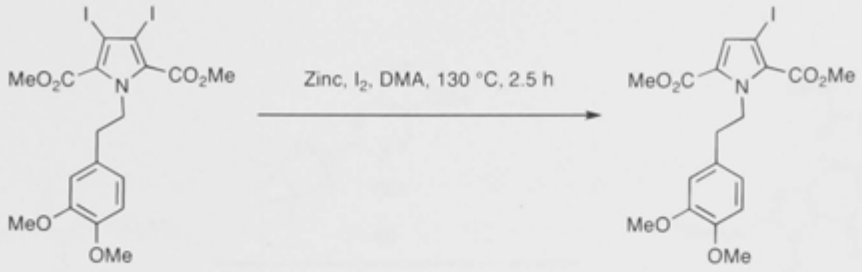
Mass Spectrum *m/z* (EI, 70 eV) 599 ($M^{+\cdot}$, 99%), 448 (18), 220 (21), 164 (100), 151 (96).

HRMS Found: $M^{+\cdot}$, 598.9300. $C_8H_7{}^{127}I_2NO_4$ requires $M^{+\cdot}$, 598.9302.

Melting Point 125-129 °C.

Elemental Analysis Calcd for $C_{18}H_{19}I_2NO_6$: C, 36.08; H, 3.20; N, 2.34. Found: C, 36.41; H, 3.31; N, 3.31.

Dimethyl 1-(3,4-dimethoxyphenethyl)-3-iodo-1*H*-pyrrole-2,5-dicarboxylate (105)



102 105

Molecular iodine (18 mg, 0.07 mmol) was added, under nitrogen, to zinc powder (52 mg, 0.80 mmol) and stirred for 2 min then DMA (0.8 mL) was added and stirring continued for 2 min. Dimethyl 1-(3,4-dimethoxyphenethyl)-3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (**102**) (435 mg, 0.73 mmol) was added and the ensuing mixture heated to 130 °C for 2.5 h. The mixture was cooled to 18 °C, concentrated on silica (1.0 g) and subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:3 v/v pentane/diethyl ether gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v pentane/diethyl ether) furnished the *title compound* ***105*** (262 mg, 76%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1 H), 6.75 (s, 1 H), 6.74 (d, J = 1.5 Hz, 1 H), 6.64 (d, J = 1.8 Hz, 1 H), 4.96 (t, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 3.84 (s, 6 H), 3.81 (s, 3 H), 2.93 (t, J = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 160.0 (C), 148.7 (C), 147.7 (C), 130.5 (C), 128.8 (C), 127.8 (C), 126.4 (CH), 121.1 (CH), 112.2 (CH), 111.1 (CH), 68.5 (C), 55.9 (CH_3), 55.8 (CH_3), 51.8 (CH_3), 51.5 (CH_3), 49.1 (CH_2), 37.6 (CH_2).

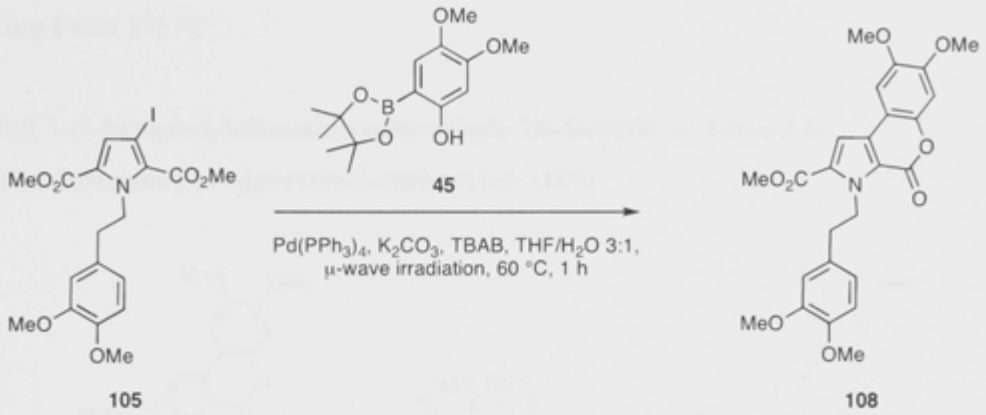
IR ν_{max} (NaCl)/cm^{-1} 2952, 1725, 1516, 1263, 1235, 1030, 809.

Mass Spectrum *m/z* (EI, 70 eV) 473 ($M^{+\cdot}$, 51%), 427 (8), 347 (31), 164 (59), 151 (100).

HRMS Found: $M^{+\cdot}$, 473.0332. $C_{18}H_{20}{}^{127}INO_6$ requires $M^{+\cdot}$, 473.0335.

Melting Point 108-110 °C.

Methyl 3-(3,4-dimethoxyphenethyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (108)



A solution of pyrrole **105** (30 mg, 0.06 mmol) in THF/H_2O (1.3 mL of 3:1 v/v mixture) was treated with potassium carbonate (38 mg, 0.27 mmol), TBAB (4 mg, 20 mol-%) and boronate ester **45** (42 mg, 0.15 mmol). The resulting mixture was flushed with nitrogen, then $Pd(PPh_3)_4$ (7 mg, 10 mol-%) was added and the reaction vessel again flushed with nitrogen then sealed. The ensuing mixture was subjected to microwave irradiation (150 W, 60 °C, 1 min ramp time) for 1 h. The cooled reaction mixture was then diluted with H_2O (20 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether → diethyl ether gradient elution). Concentration of the appropriate fractions (R_f = 0.3 in diethyl ether) furnished the *title compound* ***108*** (25 mg, 85%) as a white, crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1 H), 7.12 (s, 1 H), 6.92 (s, 1 H), 6.83 (d, J = 1.5 Hz, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 6.79 (s, 1 H), 5.15 (t, J = 8.0 Hz, 2 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.06 (t, J = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (C), 155.0 (C), 149.8 (C), 148.8 (C), 147.7 (C), 146.5 (C), 145.9 (C), 130.9 (C), 130.4 (C), 128.7 (C), 121.2 (CH), 119.2 (C), 112.3 (CH), 111.1 (CH), 109.2 (C), 108.0 (CH), 103.9 (CH), 100.6 (CH), 56.4 (CH_3), 56.2 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 52.1 (CH_3), 48.4 (CH_2), 37.8 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 2946, 2832, 1732, 1707, 1593, 1516, 1438, 1142, 1010, 770.

Mass Spectrum *m/z* (EI, 70 eV) 467 ($M^{+\cdot}$, 90%), 316 (25), 303 (71), 271 (54), 164 (100), 151 (64).

HRMS Found: $M^{+\cdot}$, 467.1582. $C_{25}H_{25}NO_8$ requires $M^{+\cdot}$, 467.1580.

Melting Point 175 °C.

Methyl 3-(2-bromo-4,5-dimethoxyphenethyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (109)

108 **109**

A magnetically stirred solution of pyrrole **108** (42 mg, 0.090 mmol) in DMF (3 mL) was cooled to –78 °C then treated, in one portion, with NBS (20 mg, 0.112 mmol) and the ensuing mixture then allowed to warm to 18 °C. After stirring at this temperature for 20 h, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL) then dried with Na_2SO_4, filtered and concentrated. The ensuing light-yellow solid was subjected to flash chromatography (silica, CH_2Cl_2 → 9:1 v/v CH_2Cl_2/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in diethyl ether) afforded the *title compound **109*** (32 mg, 65%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1 H), 7.04 (s, 1 H), 6.89 (s, 1 H), 6.84 (s, 1 H), 6.63 (s, 1 H), 5.14 (t, *J* = 7.2 Hz, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.14 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (C), 155.0 (C), 149.9 (C), 148.3 (C), 148.2 (C), 146.5 (C), 145.9 (C), 131.4 (C), 129.2 (C), 128.9 (C), 119.2 (C), 115.1 (CH), 114.6 (C),

113.6 (CH), 109.1 (C), 108.1 (CH), 103.9 (CH), 100.6 (CH), 56.4 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 55.9 (CH_3), 52.1 (CH_3), 46.7 (CH_2), 37.5 (CH_2).

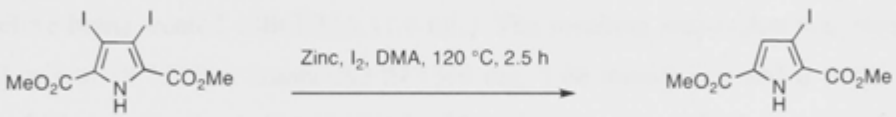
IR ν_{max} (KBr)/cm^{-1} 2930, 1734, 1707, 1511, 1435, 1410, 1259, 1222, 1136, 1039, 771.

Mass Spectrum *m/z* (EI, 70 eV) 547 ($M^{+\cdot}$, 84%), 545 (81), 467 (34), 407 (16), 316 (86), 303 (100), 271 (97).

HRMS Found: $M^{+\cdot}$, 545.0695. $C_{25}H_{24}{}^{79}BrNO_8$ requires $M^{+\cdot}$, 545.0685.

Melting Point 182-186 °C.

Dimethyl 3-iodo-1*H*-pyrrole-2,5-dicarboxylate (111)



101 **111**

Iodine (29 mg, 0.12 mmol) was added to zinc powder (86 mg, 1.32 mmol) maintained under a nitrogen atmosphere and the ensuing mixture was stirred magnetically at 18 °C for 2 min before being treated with DMA (0.8 mL). The resulting suspension was stirred for a further 2 min at 18 °C then compound **101** (500 mg, 1.15 mmol) was added to the reaction mixture which was then heated at 120 °C for 2.5 h. After this time the reaction mixture was cooled to 18 °C then treated with flash grade silica gel (3.0 g) and concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash chromatography (silica, 6:1 v/v pentane/diethyl ether → 1:2 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 1:3 v/v pentane/diethyl ether) gave the *title compound **111*** (247 mg, 69%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (broad s, 1 H), 7.03 (s, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 159.8 (C), 126.9 (C), 126.3 (C), 124.5 (CH), 68.6 (C), 52.3 (CH_3), 52.1 (CH_3).

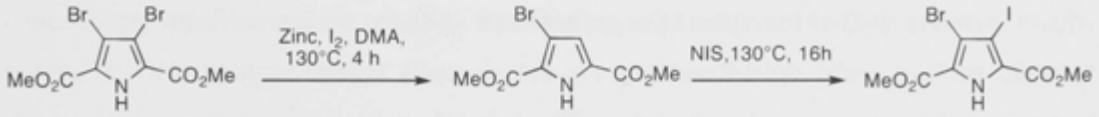
IR ν_{max} (KBr)/cm^{-1} 3440, 3280, 2953, 1729, 1703, 1544, 1438, 1272, 776.

Mass Spectrum *m/z* (EI, 70 eV) 309 ($M^{+\cdot}$, 100%), 277 (34), 246 (79), 219 (53), 199 (12).

HRMS Found: $M^{+\cdot}$, 308.9495. $C_8H_8{}^{127}INO_4$ requires $M^{+\cdot}$, 308.9498.

Melting Point 139-140 °C.

Dimethyl 3-bromo-4-iodo-1*H*-pyrrole-2,5-dicarboxylate (112)



97 **113** **112**

Iodine (38 mg, 0.15 mmol) was added to zinc powder (101 mg, 1.55 mmol) maintained under a nitrogen atmosphere and the ensuing mixture was stirred magnetically at 18 °C for 2 min before being treated with DMA (1.6 mL). The resulting suspension was stirred for a further 3 min at 18 °C then compound **97** (500 mg, 1.48 mmol) was added to the reaction mixture which was then heated at 130 °C for 2 h. After this time, a further equivalent of zinc powder was added, stirring continued for 2 h then additional zinc powder (50 mg) was added. The resulting mixture was cooled to 18 °C and a small amount was removed by pipette from the mixture, concentrated on silica and subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:3 v/v pentane/diethyl ether gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in 1:3 v/v pentane/diethyl ether) furnished a pure sample of compound **113** as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (bs, 1 H), 6.91 (s, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 (C), 159.7 (C), 125.2 (C), 123.3 (C), 118.8 (CH), 103.5 (C), 52.3 (CH_3), 52.2 (CH_3).

IR ν_{max} (KBr)/cm^{-1} 3276, 2956, 1731, 1704, 1429, 1274, 1208, 1009, 776.

Mass Spectrum *m/z* (EI, 70 eV) 263 and 261 ($M^{+\cdot}$, 97 and 100%), 232 and 230 (21 and 22), 200 and 198 (87 and 88), 171 and 173 (38 and 39).

HRMS Found: $M^{+\cdot}$, 262.9604. $C_8H_8{}^{81}BrNO_4$ requires $M^{+\cdot}$, 262.9616.

Melting Point 166-168 °C.

This sample was added back into the bulk reaction mixture, NIS (0.50 g, 2.21 mmol) was added and stirring was continued for 14 h. To ensure full conversion, further NIS (0.50 g, 2.21 mmol) was added, followed by DMF (2 mL). After stirring for 16 h, the reaction mixture was diluted with water (30 mL), washed with $Na_2S_2O_3$ (1 × 10 mL of a saturated

aqueous solution) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing yellow solid was concentrated on silica and the resulting free-flowing solid subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:3 v/v pentane/diethyl ether gradient elution). Concentration of the appropriate fractions (R_f = 0.3 in 1:3 v/v pentane/diethyl ether) furnished the *title compound* ***112*** (133 mg, 23% over two steps) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (bs, 1 H), 3.94 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 (C), 159.7 (C), 125.2 (C), 123.3 (C), 118.8 (C), 103.5 (C), 52.3 (CH_3), 52.2 (CH_3).

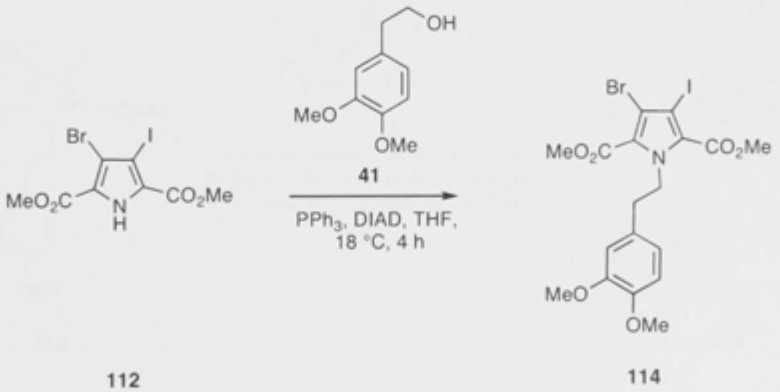
IR ν_{max} (KBr)/cm^{-1} 3266, 2951, 1719, 1696, 1436, 1272, 1041, 948, 740.

Mass Spectrum *m/z* (EI, 70 eV) 389 and 387 ($M^{+\cdot}$, 99 and 100%), 357 and 355 (39 and 40), 326 and 324 (57 and 58), 299 and 297 (37 and 38).

HRMS Found: $M^{+\cdot}$, 388.8586. $C_8H_7{}^{81}Br^{127}INO_4$ requires $M^{+\cdot}$, 388.8583.

Melting Point 207-209 °C.

Dimethyl 3-bromo-1-(3,4-dimethoxyphenethyl)-4-iodo-1*H*-pyrrole-2,5-dicarboxylate (114)



112 **114**

A solution of dimethyl 3-bromo-4-iodo-1*H*-pyrrole-2,5-dicarboxylate (**112**) (169 mg, 0.44 mmol) in THF (8 mL) was treated with triphenylphosphine (137 mg, 0.52 mmol), 3,4-dimethoxyphenethyl alcohol (**41**) (95 mg, 0.52 mmol) and diisopropyl azodicarboxylate (DIAD) (106 mg, 0.52 mmol) and the ensuing mixture was stirred for 4 h at 18 °C. The

reaction mixture was then concentrated onto flash chromatography grade silica (1.0 g) and the resulting free-flowing solid subjected to flash chromatography (silica, dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.3) furnished the *title compound* ***114*** (226 mg, 94%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J = 8.1 Hz, 1 H), 6.67 (dd, J = 8.1 and 2.1 Hz, 1 H), 6.56 (d, J = 1.8 Hz, 1 H), 4.90 (t, J = 7.2 Hz, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.93 (t, J = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (2 × C), 148.9 (C), 147.9 (C), 130.1 (C), 129.1 (C), 126.1 (C), 121.1 (CH), 112.9 (C), 112.1 (CH), 111.3 (CH), 79.0 (C), 56.0 (CH_3), 55.8 (CH_3), 52.0 (CH_3), 51.8 (CH_3), 50.2 (CH_2), 37.7 (CH_2).

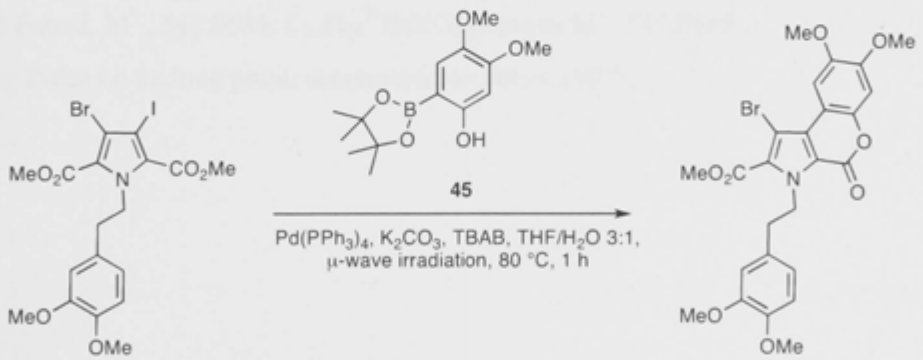
IR ν_{max} (NaCl)/cm^{-1} 2952, 1721, 1515, 1262, 1238, 1169, 1029, 776.

Mass Spectrum *m/z* (EI, 70 eV) 553 and 551 ($M^{+\cdot}$, 22 and 22%), 164 (49), 151 (100).

HRMS Found: $M^{+\cdot}$, 550.9443. $C_{18}H_{19}{}^{79}Br^{127}INO_6$ requires $M^{+\cdot}$, 550.9441.

Melting Point 125-129 °C.

Methyl 1-bromo-3-(3,4-dimethoxyphenethyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (100)



A 10 mL microwave pressure vial containing a solution of pyrrole **114** (30 mg, 0.054 mmol) in THF/H_2O (1.3 mL of 3:1 v/v mixture) was treated with potassium carbonate (76 mg, 0.550 mmol), TBAB (4 mg, 20 mol-%), and boronate ester **45** (40 mg, 0.143 mmol). The resulting mixture was flushed with nitrogen, then $Pd(PPh_3)_4$ (6 mg, 10 mol-%) was added and the reaction vessel again flushed with nitrogen then sealed. The reaction mixture was

subjected to microwave irradiation (150 W, 80 °C, 1 min ramp time) for 1 h then cooled, diluted with H_2O (20 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 6:1 v/v pentane/diethyl ether → 1:9 v/v pentane/diethyl ether gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:3 v/v pentane/diethyl ether) furnished the *title compound* ***100*** (15 mg, 51%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 6.93 (s, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.73 (s, 1 H), 6.73 (d, J = 5.2 Hz, 1 H), 5.09 (t, J = 7.2 Hz, 2 H), 3.99 (s, 3 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.03 (t, J = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (C), 154.2 (C), 149.9 (C), 148.9 (C), 147.8 (C), 146.1 (C), 145.9 (C), 130.1 (C), 130.0 (C), 126.3 (C), 121.1 (CH), 118.0 (C), 112.2 (CH), 111.2 (CH), 108.9 (C), 104.3 (CH), 100.4 (CH), 95.7 (C), 56.3 (CH_3), 56.2 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 52.3 (CH_3), 49.4 (CH_2), 37.8 (CH_2).

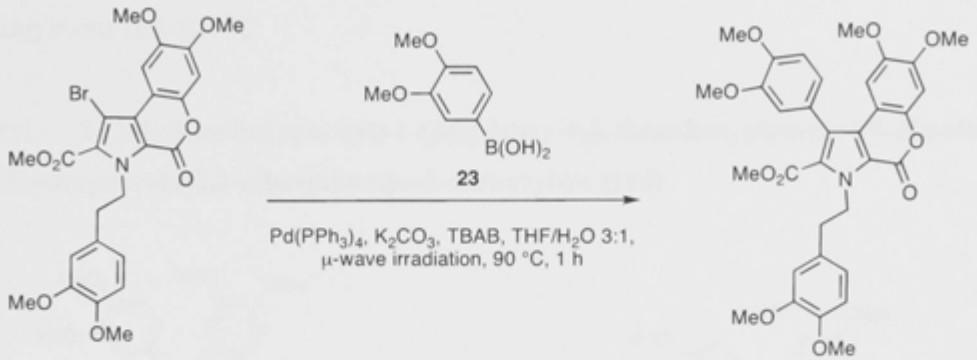
IR ν_{max} (KBr)/cm^{-1} 2925, 2850, 1728, 1514, 1462, 1263, 1233, 1158, 1040.

Mass Spectrum *m/z* (EI, 70 eV) 547 and 545 ($M^{+\cdot}$, 33 and 32%), 383 and 381 (20 and 20), 351 and 349 (25 and 25), 164 (100), 151 (64).

HRMS Found: $M^{+\cdot}$, 545.0686. $C_{25}H_{24}{}^{79}BrNO_8$ requires $M^{+\cdot}$, 545.0685.

Melting Point no melting point, decomposition above 190 °C.

Methyl 3-(3,4-dimethoxyphenethyl)-1-(3,4-dimethoxyphenyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (91)



A solution of pyrrole **100** (31 mg, 0.06 mmol) in THF/H_2O (1.3 mL of 3:1 v/v mixture) was treated with potassium carbonate (32 mg, 0.23 mmol), TBAB (4 mg, 20 mol %) and boronic acid **23** (32 mg, 0.12 mmol). The resulting mixture was flushed with nitrogen then treated with $Pd(PPh_3)_4$ (7 mg, 10 mol %), flushed again with nitrogen then sealed and subjected to microwave irradiation (150 W, 90 °C, 1 min ramp time) for 1 h. The cooled reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (4 × 30 mL) then the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:6 v/v pentane/diethyl ether → diethyl ether → 1:1 diethyl ether/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.2 in diethyl ether) furnished the *title compound* ***91***[8] (28 mg, 80%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.1 Hz, 1 H), 6.93-6.88 (complex m, 1 H), 6.89 (s, 1 H), 6.85 (d, *J* = 3.0 Hz, 1 H), 6.80 (m, 3 H), 6.52 (s, 1 H), 5.11 (t, *J* = 8.4 Hz, 2 H), 3.94 (s, 3 H), 3.89 (s, 3 H), 3.86 (m, 6 H), 3.85 (s, 3 H), 3.58 (s, 3 H), 3.43 (s, 3 H), 3.11 (t, *J* = 8.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (C), 155.1 (C), 149.2 (C), 148.8 (C), 148.7 (C), 148.6 (C), 147.7 (C), 146.0 (C), 145.7 (C), 130.5 (C), 129.4 (C), 126.9 (C), 126.7 (C), 124.2 (C), 122.6 (CH), 121.1 (CH), 117.5 (C), 113.3 (CH), 112.3 (CH), 111.1 (CH), 110.8 (CH), 109.5 (C), 104.5 (CH), 100.3 (CH), 56.1 (CH_3), 56.0 (2 x CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.5 (CH_3), 51.8 (CH_3), 48.7 (CH_2), 37.9 (CH_2).

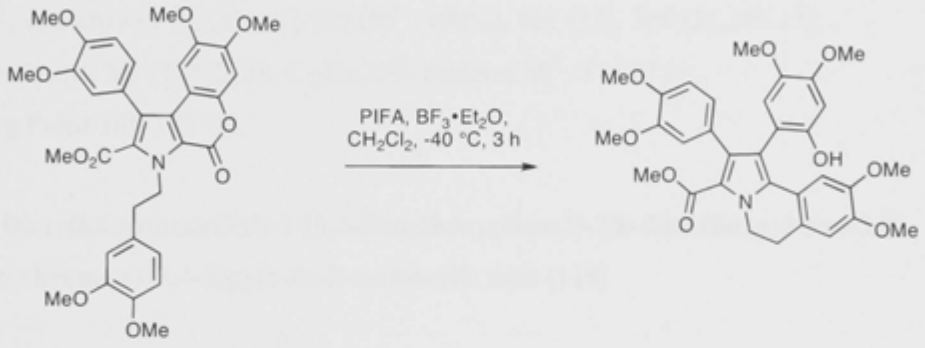
IR ν_{max} (KBr)/cm^{-1} 2935, 2833, 1729, 1703, 1515, 1444, 1265, 1218, 1155, 1028, 727.

Mass Spectrum *m/z* (EI, 70 eV) 603 ($M^{+\cdot}$, 100%), 452 (36), 439 (34), 407 (64), 151 (43).

HRMS Found: $M^{+\cdot}$, 603.2108. $C_{33}H_{33}NO_{10}$ requires $M^{+\cdot}$, 603.2104.

Melting Point 192-194 °C.

Methyl 2-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4,5-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (115)



91 **115**

Boron trifluoride diethyl etherate (12 mg, 0.08 mmol) was added to a magnetically stirred solution of PIFA (35 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (15 mL) maintained under nitrogen and the resulting solution was cooled to 0 °C then added, *via* cannula, to a magnetically stirred solution of pyrrole **91** (41 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (15 mL) maintained at –40 °C (MeCN/dry ice). The ensuing mixture was stirred at –40 °C for 2 h and then treated with ammonia (2 mL of a 12% aqueous solution) and water (8 mL) before being extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing purple oil was subjected to flash chromatography (silica, 1:6 v/v pentane/diethyl ether → diethyl ether → 1:1 diethyl ether/ethyl actetate gradient elution) and concentration of the appropriate fractions (R_f = 0.1 in diethyl ether) furnished the *title compound* ***115*** (8 mg, 20%) as a purple, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1 H), 6.74 (s, 1 H), 6.72 (s, 1 H), 6.69 (s, 1 H), 6.66 (s, 1 H), 6.54 (s, 1 H), 6.50 (s, 1 H), 4.82 (s, 1 H), 4.58-4.65 (m, 1 H), 4.64-4.55 (m, 1 H),

3.88 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.38 (s, 3 H), 3.12-3.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (C), 149.8 (C), 148.5 (C), 148.3 (C), 147.7 (2 × C), 143.1 (C), 133.7 (C), 132.3 (C), 126.8 (C), 125.6 (CH), 122.5 (2 × C), 120.2 (C), 118.8 (C), 114.8 (CH), 113.8 (C), 113.3 (CH), 111.8 (C), 110.6 (CH), 110.1 (CH), 107.6 (CH), 99.6 (CH), 56.5 (CH_3), 55.92 (CH_3), 55.87 (CH_3), 55.63 (CH_3), 55.61 (CH_3), 55.2 (CH_3), 51.1 (CH_3), 43.1 (CH_2), 28.9 (CH_2).

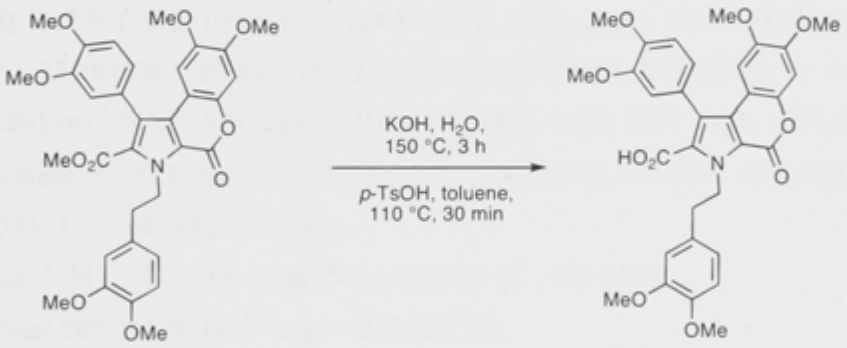
IR ν_{max} (KBr)/cm^{-1} 3445, 2924, 2849, 1688, 1438, 1261, 1134, 1026, 864.

Mass Spectrum *m/z* (EI, 70 eV) 575 ($M^{+\cdot}$, 100%), 561 (22), 368 (3), 288 (5).

HRMS Found: $M^{+\cdot}$, 575.2158. $C_{32}H_{33}NO_9$ requires $M^{+\cdot}$, 575.2155.

Melting Point 166-172 °C.

3-(3,4-Dimethoxyphenethyl)-1-(3,4-dimethoxyphenyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylic acid (119)



91 **119**

Following the procedure detailed by Steglich *et al.*,[9] a finely-ground sample of pyrrole **91** (41 mg, 0.07 mmol) was suspended in a freshly prepared and degassed solution of KOH (1.685 g, 0.03 mol) in water (2.6 mL, 0.14 mol). The resulting mixture was heated for 3 h at 150 °C and the methanol so formed was removed by continuous distillation. The reaction mixture was then cooled to 0 °C, acidified by the dropwise addition of HCl (37% w/v aqueous solution) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a deep-yellow oil. This oil was dissolved in toluene (9 mL) and the resulting solution treated with *p*-TsOH monohydrate (5 mg) and 4 Å molecular

sieves (73 mg) then heated at reflux for 0.5 h. After cooling, filtration and evaporation of the solvent, the residue was dissolved in ethyl acetate (10 mL) and the ensuing solution washed with aqueous potassium hydrogensulfate (1 × 2 mL of a 1.1 M aqueous solution) and brine (1 × 5 mL). After drying (Na_2SO_4) and filtration the filtrate was concentrated under reduced pressure and the ensuing light-yellow solid subjected to flash chromatography (silica, $CHCl_3$ → 9:1 v/v CH_2Cl_2/methanol gradient elution). Concentration of the appropriate fractions (R_f= 0.2 in 9:1 v/v CH_2Cl_2/methanol) afforded the *title compound* ***119***[6, 9] (23 mg, 57%) as a white, crystalline solid.

^{1}H NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 6.94-6.68 (complex m, 7 H), 6.43 (s, 1 H), 5.03 (t, *J* = 7.5 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.78(4) (s, 3 H), 3.77(6) (s, 3 H), 3.76 (s, 3 H), 3.34 (s, 3 H), 3.04 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, 5% CD_3OD in $CDCl_3$) δ 162.5 (C), 155.5 (C), 149.1 (C), 148.7(0) (C), 148.6(8) (C), 148.5 (C), 147.6 (C), 145.8 (C), 145.6 (C), 130.8 (C), 130.5 (C), 127.1 (C), 127.0 (C), 124.2 (C), 122.7 (CH), 121.1 (CH), 117.1 (C), 113.6 (CH), 112.3 (CH), 111.3 (CH), 111.0 (CH), 109.6 (C), 104.5 (CH), 100.3 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.81 (CH_3), 55.78 (CH_3), 55.60 (CH_3), 55.3 (CH_3), 48.7 (CH_2), 37.8 (CH_2).

IR ν_{max} (KBr)/cm^{-1} 3436, 2921, 2851, 1716, 1515, 1465, 1260, 1231, 1156, 1027, 769.

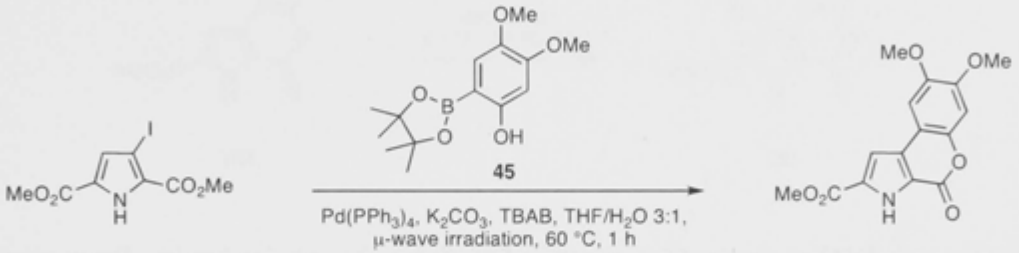
Mass Spectrum *m/z* (EI, 70 eV) 589 ($M^{+\cdot}$, 28%), 545 (100), 425 (14), 407 (19), 394 (52), 381 (87), 334 (11), 164 (33), 151 (56).

HRMS Found: $M^{+\cdot}$, 589.1944. $C_{32}H_{31}NO_{10}$ requires $M^{+\cdot}$, 589.1948.

Melting Point 209-211 °C (lit.[6] m.p. = 219-220 °C).

5.4 Specific Experimental Procedures and Characterisation Data Associated with the Compounds Described in Chapter 4

Methyl 7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (122)



111 122

A solution of pyrrole **111** (111 mg, 0.36 mmol) in THF/H_2O (7.2 mL of 3:1 v/v mixture) was treated with potassium carbonate (213 mg, 1.54 mmol), TBAB (22 mg, 20 mol %), and boronate ester **45** (241 mg, 0.86 mmol). The resulting mixture was flushed with nitrogen, then $Pd(PPh_3)_4$ (41 mg, 10 mol-%) was added and the reaction vessel again flushed with nitrogen before being sealed then subjected to microwave irradiation (150 W, 60 °C, 1 min ramp time) for 1 h. The cooled reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing yellow solid was washed with dichloromethane to give the *title compound* ***122*** (98 mg, 90%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1 H), 7.26 (s, 1 H), 7.14 (s, 1 H), 6.95 (s, 1 H), 3.981 (s, 3 H), 3.977 (s, 3 H), 3.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 155.1 (C), 149.9 (C), 146.6 (C), 146.2 (C), 130.6 (C), 129.8 (C), 118.7 (C), 109.3 (C), 107.0 (CH), 104.2 (CH), 101.0 (CH), 56.4 (CH_3), 56.3 (CH_3), 52.6 (CH_3).

IR ν_{max} (KBr)/cm^{-1} 3441, 3288, 2953, 2924, 2463, 1735, 1278, 1144, 772.

Mass Spectrum *m/z* (EI, 70 eV) 303 ($M^{+\cdot}$, 17%), 256 (19), 149 (26), 97 (36), 69 (61), 43 (100).

HRMS Found: $M^{+\cdot}$, 303.0744. $C_{15}H_{13}NO_6$ requires $M^{+\cdot}$, 303.0743.

Melting Point 253-258 °C.

Methyl 1-bromo-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (121)

122 **121**

A magnetically stirred solution of pyrrole **122** (100 mg, 0.33 mmol) in DMF (2.5 mL) was cooled to 0 °C then treated, in one portion, with NBS (70 mg, 0.396 mmol) and the ensuing mixture allowed to warm to 18 °C. After stirring at this temperature for 12 h, another aliquot of NBS (70 mg) was added and the reaction mixture heated at 50 °C for 4 h. The cooled reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with water (1 × 30 mL) and brine (1 × 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow solid was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether → diethyl ether → ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.5 in diethyl ether) furnished the *title compound* ***121*** (75 mg, 59%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 8.12 (s, 1 H), 6.95 (s, 1 H), 4.02 (s, 3 H), 4.00 (s, 3 H), 3.95 (s, 3 H).

^{13}C NMR (125 MHz, 5% $(CD_3)_2SO$ in $CDCl_3$) δ 159.9 (C), 154.5 (C), 149.6 (C), 146.0 (C), 145.9 (C), 128.1 (C), 126.3 (C), 118.4 (C), 109.2 (C), 104.1 (CH), 100.7 (CH), 96.0 (C), 56.2 (CH_3), 56.1 (CH_3), 52.3 (CH_3).

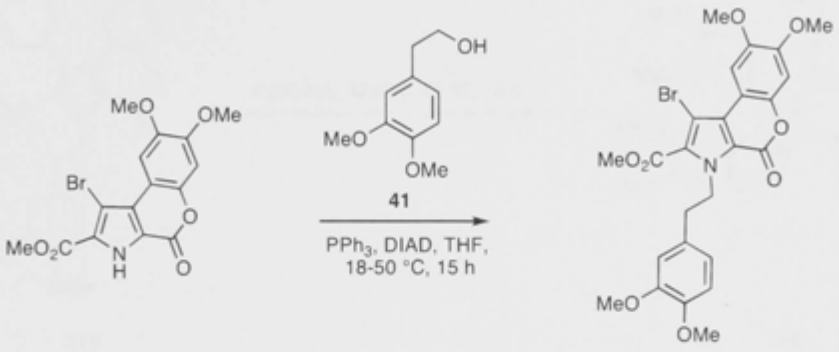
IR ν_{max} (KBr)/cm^{-1} 3412, 3223, 2925, 1705, 1495, 1280, 704.

Mass Spectrum *m/z* (EI, 70 eV) 383 and 381 ($M^{+\cdot}$, both 71%), 351 and 349 (100 and 99), 336 and 334 (29 and 30), 308 and 306 (14 and 15), 227 (20).

HRMS Found: $M^{+\cdot}$, 380.9848. $C_{15}H_{12}{}^{79}BrNO_6$ requires $M^{+\cdot}$, 380.9848.

Melting Point no melting point, decomposition above 280 °C.

Methyl 1-bromo-3-(3,4-dimethoxyphenethyl)-7,8-dimethoxy-4-oxo-3,4-dihydrochromeno[3,4-b]pyrrole-2-carboxylate (100)

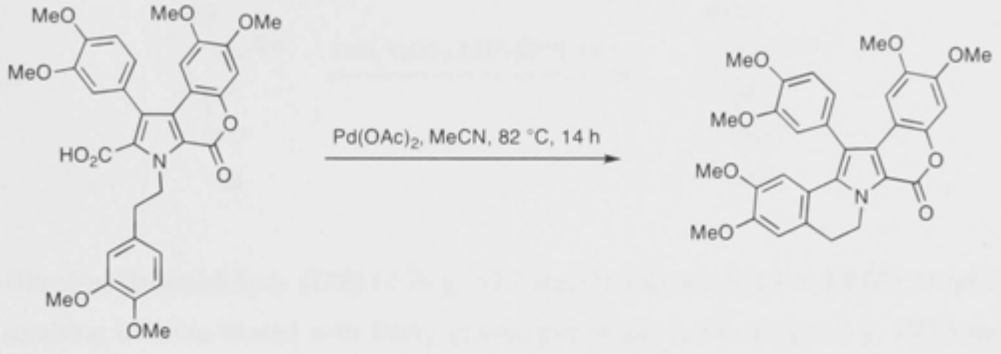


121 100

A solution of pyrrole **121** (75 mg, 0.20 mmol) in THF (5 mL) was treated with triphenylphosphine (62 mg, 0.24 mmol), alcohol **41** (43 mg, 0.236 mmol) and DIAD (48 mg, 0.24 mmol). The ensuing mixture was stirred at 18 °C for 14 h then heated at 50 °C for 1 h. The resulting mixture was cooled then treated with flash chromatography grade silica gel (600 mg) before being concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash chromatography (silica, dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.3) gave the *title compound* ***100*** (66 mg, 62%) as a white, crystalline solid.

This material was identical, in all respects, with an authentic sample of compound **100** obtained *via* the procedure detailed above.

Lamellarin G Trimethyl Ether (55)



119 55

Following the procedure outlined by Iwao *et al.*,[8] a magnetically stirred solution of pyrrole **119** (11 mg, 0.019 mmol) and palladium acetate (5 mg, 0.021 mmol) in acetonitrile (1 mL) was heated at 82 °C for 14 h. After cooling the reaction mixture to 18 °C, it was subjected to flash chromatography (silica, 19:1 v/v CH_2Cl_2/ethyl acetate → 4:1 v/v CH_2Cl_2/ethyl acetate gradient elution) and concentration of the appropriate fractions ($R_f = 0.5$ in 9:1 v/v CH_2Cl_2/methanol) furnished lamellarin G trimethyl ether (**55**) (5 mg, 48%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.4 and 2.0 Hz, 1 H), 7.08 (d, J = 8.0 Hz, 1 H), 7.05 (d, J = 2.0 Hz, 1 H), 6.91 (s, 1 H), 6.76 (s, 1 H), 6.72 (s, 1 H), 6.66 (s, 1 H), 4.86-4.72 (m, 2 H), 3.96 (s, 3 H), 3.89 (m, 6 H), 3.86 (s, 3 H), 3.46 (s, 3 H), 3.37 (s, 3 H), 3.13 (t, J = 7.2 Hz, 2 H).

^{13}C NMR (200 MHz, $CDCl_3$) δ 155.6 (C), 149.7 (C), 149.0 (C), 148.8 (C), 148.8 (C), 147.5 (C), 146.1 (C), 145.5 (C), 136.0 (C), 128.2 (C), 128.0 (C), 126.6 (C), 123.6 (CH), 120.0 (C), 114.8 (C), 113.9 (CH), 113.8 (C), 111.8 (CH), 111.0 (CH), 110.3 (C), 108.6 (CH), 104.5 (CH), 100.5 (CH), 56.2 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 56.1 (CH_3), 55.9 (CH_3), 55.5 (CH_3), 55.2 (CH_3), 42.4 (CH_2), 28.7 (CH_2).

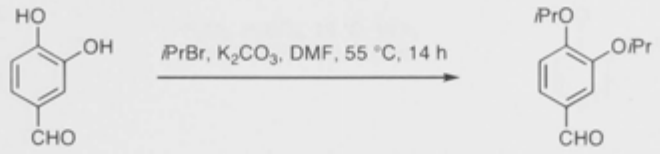
IR ν_{max} (KBr)/cm^{-1} 3435, 2925, 2851, 1706, 1619, 1580, 1545, 1514, 1486, 1463, 1414, 1338, 1263, 1240, 1213, 1165, 1039.

Mass Spectrum *m/z* (ESI) 567 [$(M+Na)^+$, 39%], 545 [$(M+H)^+$, 100], 414 (44), 302 (76), 149 (49).

HRMS Found: $(M+Na)^+$, 566.1789. $C_{32}H_{29}NO_8$ requires $(M+Na)^+$, 566.1791.

Melting Point 233-234 °C (lit.[10] m.p. = 238-239 °C).

3,4-Diisopropoxybenzaldehyde (129)



128 **129**

3,4-Dihydroxybenzaldehyde (**128**) (8.78 g, 63.6 mmol) was dissolved in DMF (20 mL) and the resulting solution treated with finely ground potassium carbonate (27.3 g, 197.5 mmol) and 2-bromopropane (11.1 mL, 118.5 mmol). The ensuing mixture was heated at 55 °C for 14 h in an apparatus equipped with a reflux condenser. The cooled reaction mixture was diluted with ethyl acetate (200 mL) then water (300 mL) and the separated aqueous phase extracted with ethyl acetate (4 × 150 mL). The combined organic phases were washed with water (1 × 200 mL) then concentrated under reduced pressure. The residue thus obtained was dissolved in diethyl ether (100 mL) and the resulting solution washed with water (2 × 100 mL) and brine (1 × 200 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 3,4-diisopropoxybenzaldehyde (**129**)[11] (12.54 g, 89%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 7.44 (dd, *J* = 4.8 and 1.8 Hz, 1 H), 7.43 (s, 1 H), 6.98 (d, *J* = 8.1 Hz, 1 H), 4.96 (quin, *J* = 6.6 Hz, 1 H), 4.53 (quin, *J* = 6.3 Hz, 1 H), 1.39 (d, *J* = 6.6 Hz, 6 H), 1.36 (d, *J* = 6.3 Hz, 6 H).

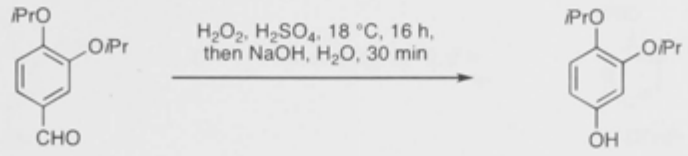
^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9 (CH), 154.9 (C), 148.9 (C), 130.0 (C), 126.4 (CH), 116.1 (CH), 114.8 (CH), 72.4 (CH), 71.8 (CH), 22.1 (2 × CH_3), 22.0 (2 × CH_3).

IR ν_{max} (NaCl)/cm^{-1} 2979, 1690, 1594, 1267, 1106, 947.

Mass Spectrum *m/z* (EI, 70 eV) 222 ($M^{+\cdot}$, 59%), 180 (39), 137 (100), 109 (25), 81 (27), 43 (81).

HRMS Found: $M^{+\cdot}$, 222.1255. $C_{13}H_{18}O_3$ requires $M^{+\cdot}$, 222.1256.

3,4-Diisopropoxyphenol (130)



129 **130**

3,4-Diisopropoxyphenol (**130**) was prepared from 3,4-diisopropoxybenzaldehyde (**129**) according to the method of Yang *et. al*[11] and isolated in 98% yield as a light-brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 9.0 Hz, 1 H), 6.44 (d, J = 3.0 Hz, 1 H), 6.31 (dd, J = 8.7 and 3.0 Hz, 1 H), 4.75 (s, 1 H), 4.45 (sept, J = 5.7 Hz, 1 H), 4.27 (sept, J = 6.6 Hz, 1 H), 1.32 (d, J = 5.7 Hz, 6 H), 1.28 (d, J = 5.7 Hz, 6 H).

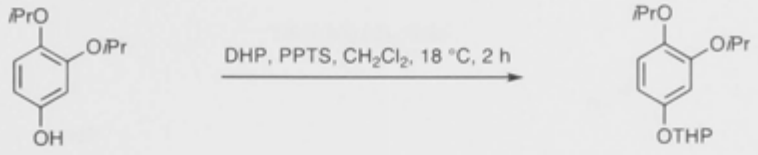
^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (C), 150.1 (C), 141.0 (C), 121.1 (CH), 107.1 (CH), 104.3 (CH), 74.2 (CH), 71.1 (CH), 22.1 (2 × CH_3), 21.9 (2 × CH_3).

IR ν_{max} (NaCl)/cm^{-1} 3372, 2976, 2932, 1601, 1507, 1110, 995.

Mass Spectrum *m/z* (EI, 70 eV) 210 ($M^{+\cdot}$, 53%), 168 (69), 127 (78), 97 (71), 43 (100).

HRMS Found: $M^{+\cdot}$, 210.1255. $C_{12}H_{18}O_3$ requires $M^{+\cdot}$, 210.1256.

2-(3,4-Diisopropoxyphenoxy)tetrahydro-2*H*-pyran (131)



130 **131**

DHP (0.8 mL, 8.48 mmol) and PPTS (71 mg, 0.28 mmol) were added to a magnetically stirred solution of 3,4-diisopropoxyphenol (**130**) (594 mg, 2.83 mmol) in dichloromethane (2 mL) maintained at 18 °C. After 2 h the reaction mixture was diluted with dichloromethane (20 mL) and water (20 mL). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give *2-(3,4-diisopropoxyphenoxy)tetrahydro-2*H*-pyran* (**131**) (830 mg, quant.) as a clear, red oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 8.7 Hz, 1 H), 6.65 (d, J = 3.0 Hz, 1 H), 6.57 (dd, J = 8.7 and 3.0 Hz, 1 H), 5.30 (t, J = 3.3 Hz, 1 H), 4.48 (quin, J = 6.6 Hz, 1 H), 4.30 (quin, J = 6.3 Hz, 1 H), 4.00-3.82 (complex m, 2 H), 3.66-3.54 (complex m, 2 H), 2.08-1.60 (complex m, 4 H), 1.33 (d, J = 6.3 Hz, 6 H), 1.29 (d, J = 6.0 Hz, 6 H).

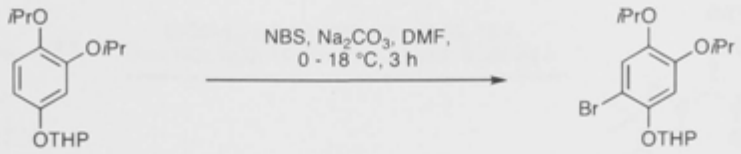
^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (C), 150.1 (C), 143.3 (C), 120.3 (CH), 108.2 (CH), 106.7 (CH), 96.9 (CH), 73.1 (CH), 71.3 (CH), 61.8 (CH_2), 30.4 (CH_2), 25.2 (CH_2), 22.2 (2 × CH_3), 22.0 (2 × CH_3), 18.8 (CH_2).

IR ν_{max} (NaCl)/cm^{-1} 2973, 2941, 1605, 1502, 1110, 965.

Mass Spectrum *m/z* (EI, 70 eV) 294 ($M^{+\cdot}$, 15%), 210 (60), 168 (62), 126 (63), 85 (63), 43 (100).

HRMS Found: $M^{+\cdot}$, 294.1827. $C_{17}H_{26}O_4$ requires $M^{+\cdot}$, 294.1831.

2-(2-Bromo-4,5-diisopropoxyphenoxy)tetrahydro-2*H*-pyran (132)



131 **132**

Compound **131** (830 mg, 2.82 mmol) and sodium carbonate (2.00 g) were dissolved in DMF (10 mL) and the resulting solution cooled to 0 °C then treated, in portions, with NBS (702 mg, 3.95 mmol). After 1 h the ice-bath was removed and stirring continued for another 2 h. Ethyl acetate (50 mL) and water (20 mL) were then added to the reaction mixture and the phases separated. The aqueous phase was extracted with ethyl acetate (4 × 50 mL) and the combined organic phases were then washed with water (1 × 50 mL) before being concentrated under reduced pressure. The residue thus obtained was taken up in ethyl ether (100 mL) and the resulting solution washed with water (2 × 50 mL) then brine (1 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was then taken up in pentane (200 mL) then filtered (to remove residual succinimide) and concentrated under reduced pressure to give the *title compound **132*** (900 mg, 86%) as a white, crystalline solid.

^{1}H NMR (400 MHz, C_6D_6) δ 7.19 (s, 1 H), 6.99 (s, 1 H), 5.17 (t, J = 2.8 Hz, 1 H), 4.26 (sept, J = 6.0 Hz, 1 H), 4.02 (sept, J = 6.4 Hz, 1 H), 3.78 (dt, J = 10.8 and 2.8 Hz, 1 H), 3.31 (td, J = 10.8 and 4.4 Hz, 1 H), 2.01-1.88 (complex m, 1 H), 1.82-1.72 (complex m, 1 H), 1.56-1.44 (complex m, 1 H), 1.36-1.22 (complex m, 2 H), 1.18-1.15 (complex m, 1 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.08 (d, J = 6.0 Hz, 3 H), 1.04 (d, J = 6.0 Hz, 6 H).

^{13}C NMR (75 MHz, C_6D_6) δ 149.4 (C), 148.7 (C), 144.5 (C), 122.8 (CH), 107.9 (CH), 103.4 (C), 97.3 (CH), 72.5 (CH), 71.6 (CH), 61.1 (CH_2), 30.2 (CH_2), 25.2 (CH_2), 21.9 (2 × CH_3), 21.8 (2 × CH_3), 18.3 (CH_2).

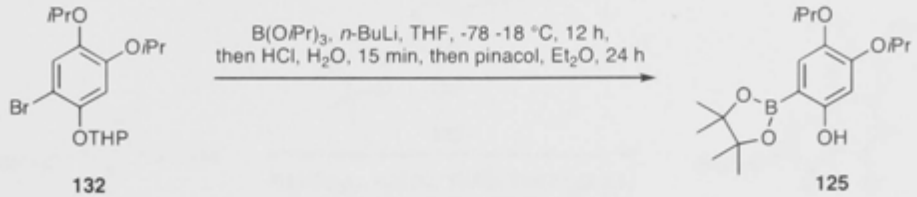
IR ν_{max} (NaCl)/cm^{-1} 2974, 2929, 1490, 1196, 1110, 960.

Mass Spectrum *m/z* (EI, 70 eV) 374 and 372 ($M^{+\cdot}$, both 2%), 290 and 288 (both 78), 246 and 244 (72 and 70), 206 and 204 (85 and 83), 85 (75), 43 (100).

HRMS Found: $M^{+\cdot}$, 374.0916. $C_{17}H_{25}{}^{81}BrO_4$ requires $M^{+\cdot}$, 374.0916.

Melting Point 48-50 °C.

4,5-Diisopropoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (125)



132 125

n-Butyllithium (1.0 mL of a 1.6 M solution in hexane, 1.57 mmol) was added, dropwise over 0.25 h, to a magnetically stirred solution of compound **132** (450 mg, 1.21 mmol) and triisopropyl borate (550 μL, 2.41 mmol) in THF (15 mL) maintained at −78 °C. Stirring was continued at this temperature for 0.66 h then the reaction mixture was allowed to warm to 18 °C over 12 h. The ensuing mixture was treated with HCl (5 mL of a 1 M aqueous solution) and after a further 0.25 h the phases were separated and the aqueous one extracted with THF (3 × 20 mL). The combined organic phases were washed with brine (1 × 50mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow, mud-like solid. This solid was dissolved in diethyl ether (20 mL) and the resulting solution treated with pinacol (300 mg, 2.54 mmol). The ensuing slurry was stirred magnetically at 18 °C for 24 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v pentane/diethyl ether → 5:1 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 3:1 v/v pentane/diethyl ether) furnished the *title compound **125*** (221 mg, 55%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 7.13 (s, 1 H), 6.42 (s, 1 H), 4.54 (quin, *J* = 6.6 Hz, 1 H), 4.24 (quin, *J* = 6.6 Hz, 1 H), 1.35 (d, *J* = 6.6 Hz, 6 H), 1.34 (s, 12 H), 1.27 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 155.0 (C), 141.4 (C), 126.6 (CH), 102.2 (CH), 84.1 (C), 74.2 (CH), 70.6 (CH), 24.8 (4 × CH_3), 22.4 (2 × CH_2), 22.0 (2 × CH_3) (signal due to sp^2-hybridized carbon bearing boron not observed).

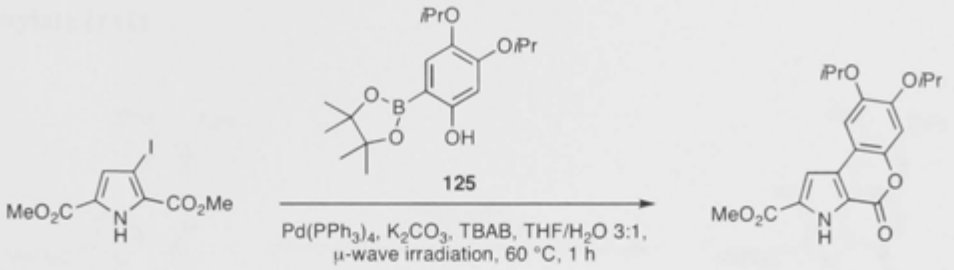
^{11}B NMR (96 MHz, $CDCl_3$) δ 30.0.

IR ν_{max} (NaCl)/cm^{-1} 3453, 2977, 2933, 1623, 1388, 1140, 1111, 963.

Mass Spectrum *m/z* (EI, 70 eV) 336 ($M^{+\cdot}$, 51%), 294 (22), 252 (35), 205 (60), 195 (100), 152 (70).

HRMS Found: $M^{+\cdot}$, 336.2109. $C_{18}H_{29}{}^{11}BO_5$ requires $M^{+\cdot}$, 336.2108.

Methyl 7,8-diisopropoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (140)



111 **140**

A mixture of pyrrole **111** (603 mg, 0.36 mmol), potassium carbonate (1.08 g, 7.81 mmol), TBAB (123 mg, 20 mol %) and boronate ester **125** (1.094 g, 3.25 mmol) in THF/H_2O (27 mL of 3:1 v/v mixture) was divided into six equal portions each of which was placed in a microwave reactor vial. The contents of each vial were flushed with nitrogen then $Pd(PPh_3)_4$ (37.3 mg, 10 mol-%) was added to each and the vials once again flushed with nitrogen before being sealed. The contents of each vial were subjected to microwave irradiation (150 W, 60 °C, 1 min ramp time) for 1 h then cooled, combined and diluted with H_2O (200 mL) before being extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow solid was subjected to flash chromatography (silica, 5:1 v/v pentane/diethyl ether → 1:1 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v pentane/diethyl ether) furnished the *title compound* ***140*** (647 mg, 92%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1 H), 7.24 (s, 1 H), 7.21 (s, 1 H), 6.95 (s, 1 H), 4.55 (quin, J = 6.4 Hz, 1 H), 4.48 (quin, J = 6.0 Hz, 1 H), 3.98 (s, 3 H), 1.38 (d, J = 6.0 Hz, 6 H), 1.36 (d, J = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (C), 155.3 (C), 150.4 (C), 147.0 (C), 145.9 (C), 130.6 (C), 129.8 (C), 118.7 (C), 112.4 (CH), 109.9 (C), 107.0 (CH), 105.1 (CH), 73.5 (CH), 72.0 (CH), 52.5 (CH_3), 22.2 (2 × CH_3), 21.9 (2 × CH_3).

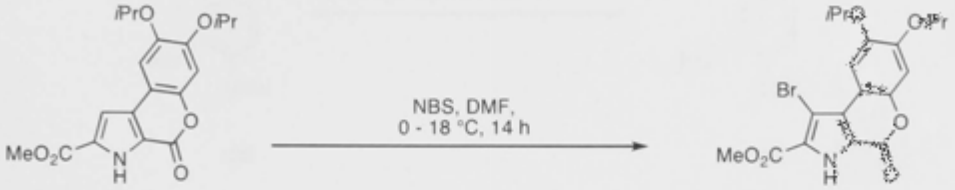
IR ν_{max} (KBr)/cm^{-1} 3445, 3261, 2975, 2930, 1737, 1710, 1278, 1108, 774.

Mass Spectrum *m/z* (EI, 70 eV) 359 ($M^{+\cdot}$, 41%), 317 (16), 275 (100), 243 (98), 98 (14), 159 (15), 43 (20).

HRMS Found: $M^{+\cdot}$, 359.1365. $C_{19}H_{21}NO_6$ requires $M^{+\cdot}$, 359.1369.

Melting Point 172-173 °C.

Methyl 1-bromo-7,8-diisopropoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (141)

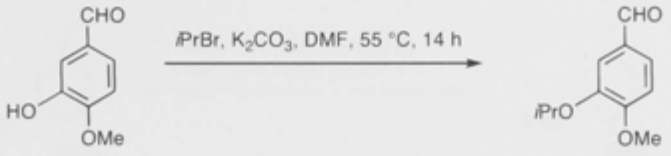


140 **141**

A magnetically stirred solution of pyrrole **140** (70 mg, 0.20 mmol) in DMF (1.5 mL) was cooled to 0 °C then treated, in one portion, with NBS (42 mg, 0.24 mmol) and the ensuing mixture allowed to warm to 18 °C, stirred at this temperature for 14 h then diluted with water (20 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with water (1 × 30 mL) and brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow solid was subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:1 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v pentane/diethyl ether) furnished the *title compound **141*** (80 mg, 94%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 8.24 (s, 1 H), 6.97 (s, 1 H), 6.95 (s, 1 H), 4.57 (quin, J = 6.3 Hz, 1 H), 4.52 (quin, J = 6.0 Hz, 1 H), 4.01 (s, 3 H), 1.40 (d, J = 6.0 Hz, 12 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (C), 154.7 (C), 150.4 (C), 146.8 (C), 145.6 (C), 127.4 (C), 126.9 (C), 117.9 (C), 111.3 (CH), 109.4 (C), 105.0 (CH), 96.9 (C), 73.3 (CH), 72.1 (CH), 52.7 (CH_3), 22.1 (2 × CH_3), 21.9 (2 × CH_3).
IR ν_{max} (KBr)/cm^{-1} 3433, 3237, 2974, 2932, 1709, 1491, 1275, 1111, 771.
Mass Spectrum *m/z* (EI, 70 eV) 439 and 437 ($M^{+\cdot}$, 6 and 6%), 355 and 353 (17 and 17), 323 and 321 (21 and 21), 277 (90), 149 (62), 69 (75), 57 (100).
HRMS Found: $M^{+\cdot}$, 437.0465. $C_{19}H_{20}{}^{79}BrNO_6$ requires $M^{+\cdot}$, 437.0474.
Melting Point no melting point, decomposition above 230 °C.

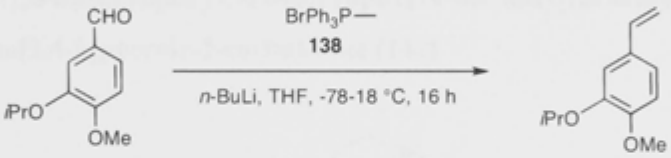
3-Isopropoxy-4-methoxybenzaldehyde (137)



136 **137**

3-Isopropoxy-4-methoxybenzaldehyde (**137**) was prepared from isovanillin according to the method of Pampín *et al.*[12] and isolated in quantitative yield as a light-yellow oil. The derived spectral data matched those reported in the literature.[12]

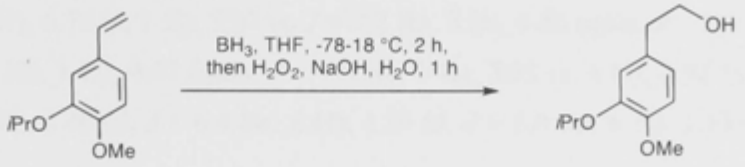
2-Isopropoxy-1-methoxy-4-vinylbenzene (139)



137 **139**

2-Isopropoxy-1-methoxy-4-vinylbenzene (**139**) was prepared from 3-Isopropoxy-4-methoxybenzaldehyde (**137**) and Wittig-salt **138** according to the method of Pampín *et al.*[12] and obtained in 82% yield as a light-yellow oil. The derived spectral data matched those reported in the literature.[12]

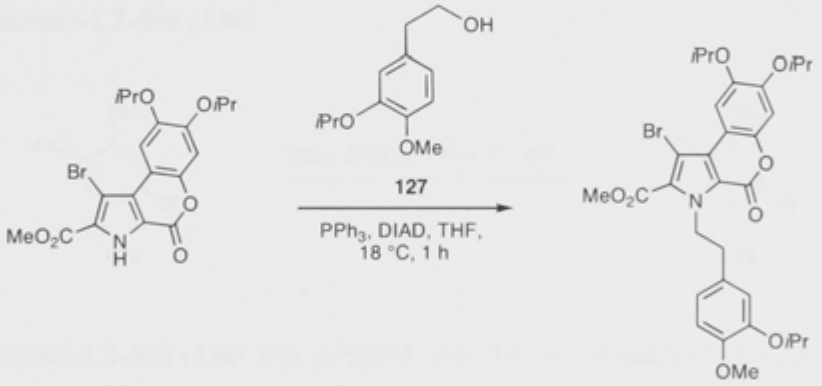
2-(3-Isopropoxy-4-methoxyphenyl)ethanol (127)



139 127

2-(3-Isopropoxy-4-methoxyphenyl)ethanol (**127**) was prepared from 2-Isopropoxy-1-methoxy-4-vinylbenzene (**139**) according to the method of Bach *et al.*[13] and isolated in 58% yield as a clear, colourless oil. The derived spectral data matched those reported in the literature.[13]

Methyl 1-bromo-7,8-diisopropoxy-3-(3-isopropoxy-4-methoxyphenethyl)-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (142)



141 142

A magnetically stirred solution of pyrrole **141** (583 mg, 1.33 mmol) in THF (20 mL) was treated with triphenylphosphine (698 mg, 2.66 mmol), compound **127** (521 mg, 2.48 mmol) and DIAD (538 mg, 2.66 mmol) and the ensuing mixture stirred at 18 °C for 1 h then treated with flash grade silica gel (2.0 g) and concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica, dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded the *title compound* ***142*** (803 mg, 96%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 6.93 (s, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 6.72 (s, 1 H), 5.07 (t, J = 7.2 Hz, 2 H), 4.56 (quin, J = 5.6 Hz, 1 H), 4.49 (quin, J = 6.4 Hz, 1 H), 4.47 (quin, J = 5.6 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.00 (t, J = 7.6 Hz, 2 H), 1.40 (d, J = 6.4 Hz, 6 H), 1.39 (d, J = 6.0 Hz, 6 H), 1.33 (d, J = 6.4 Hz, 6 H).

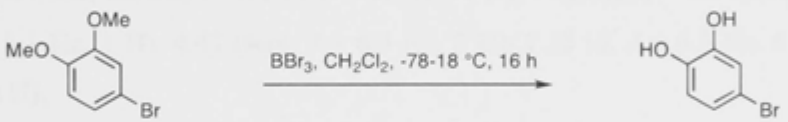
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C), 154.3 (C), 150.3 (C), 149.2 (C), 147.3 (C), 146.7 (C), 145.3 (C), 130.1 (C), 129.9 (C), 126.3 (C), 121.5 (CH), 117.9 (C), 116.5 (CH), 112.1 (CH), 111.9 (CH), 109.3 (C), 104.5 (CH), 95.9 (C), 73.3 (CH), 72.0 (CH), 71.4 (CH), 56.1 (CH_3), 52.2 (CH_3), 49.3 (CH_2), 37.7 (CH_2), 22.1 (2 × CH_3), 22.1 (2 × CH_3), 21.9 (2 × CH_3).

IR ν_{max} (NaCl)/ cm^{-1} 2976, 2932, 1732, 1507, 1266, 1157, 1109, 1011, 935.

Mass Spectrum *m/z* (EI, 70 eV) 631 and 629 ($M^{+\cdot}$, 100 and 98%), 589 and 587 (9 and 8), 547 and 545 (11 and 10), 395 and 393 (21 and 23), 353 and 351 (82), 323 and 321 (both 38).

HRMS Found: $M^{+\cdot}$, 631.1605. $C_{31}H_{36}{}^{81}BrNO_8$ requires $M^{+\cdot}$, 631.1604.

4-Bromobenzene-1,2-diol (134)



133 **134**

4-Bromobenzene-1,2-diol (**134**) was prepared from 4-bromoveratrol (**133**) according to the method of Hille *et al.*[14] and obtained in 73% yield. In contrast to Hille *et al.*, compound **134** was obtained as a white, crystalline solid, rather than an oil. The derived spectral data matched those reported in the literature.[14]

Melting Point 81-84 °C.

4-Bromo-1,2-diisopropoxybenzene (135)

134 **135**

A magnetically stirred solution of 4-bromobenzene-1,2-diol (**134**) (1.42 g, 7.53 mmol) in DMF (8 mL) was treated with finely ground potassium carbonate (5.21 g, 37.7 mmol) and 2-bromopropane (2.12 mL, 22.6 mmol). The resulting mixture was heated at 55 °C in an apparatus fitted with a reflux condenser for 14 h then cooled and diluted with ethyl acetate (50 mL) and water (50 mL). The separated aqueous phase was extracted with ethyl acetate (4 × 30 mL) and the combined organic phases were washed with water (1 × 30 mL) before being concentrated under reduced pressure. The residue was taken up in diethyl ether (50 mL) and the resulting solution washed with water (2 × 40 mL) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 4-bromo-1,2-diisopropoxybenzene (**135**) (1.81 g, 88%) as a clear, red oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 2.4 Hz, 1 H), 7.00 (dd, J = 9.3 and 2.1 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 4.43 (sept, J = 6.3 Hz, 2 H), 1.33 (d, J = 6.3 Hz, 6 H), 1.31 (d, J = 6.6 Hz, 6 H).

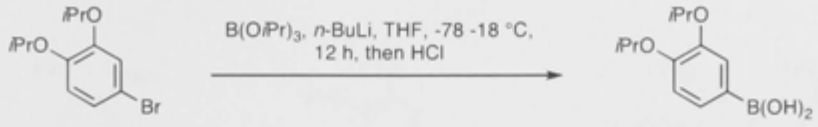
^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (C), 148.3 (C), 124.3 (CH), 120.8 (CH), 119.6 (CH), 113.5 (C), 72.5 (CH), 72.3 (CH), 22.1 (2 x CH_3), 22.1 (2 x CH_3).

IR ν_{max} (NaCl)/cm^{-1} 2976, 2931, 1584, 1488, 1257, 1107, 957.

Mass Spectrum *m/z* (EI, 70 eV) 274 and 272 ($M^{+\cdot}$, both 42%), 232 and 230 (21 and 22), 189 and 187 (both 100), 161 and 159 (both 12), 109 (14), 79 (19), 44 (57).

HRMS Found: $M^{+\cdot}$, 272.0413. $C_{12}H_{17}{}^{79}BrO_2$ requires $M^{+\cdot}$, 272.0412.

3,4-Diisopropoxyphenylboronic acid (126)



135 126

n-Butyllithium (7.0 mL of a 1.6 M solution in hexane, 11.27 mmol) was added, dropwise over 0.25 h, to a magnetically stirred solution of 4-bromo-1,2-diisopropoxybenzene **(135)** (1.54 g, 5.63 mmol) and triisopropylborate (2.6 mL, 11.27 mmol) in THF (30 mL) maintained at −78 °C. Stirring was continued at this temperature for 0.66 h, then the reaction mixture was warmed to 18 °C over 12 h and treated with HCl (25 mL of a 1 M aqueous solution). After a further 0.25 h the separated aqueous phases was extracted with THF (3 × 30 mL) and the combined organic phases were washed with brine (1 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow solid. Subjection of this material to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:3 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in 1:3 v/v pentane/diethyl ether) gave the *title compound **126*** (882 mg, 66%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.5 and 1.2 Hz, 1 H), 7.75 (d, J = 1.2 Hz, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 4.64 (quin, J = 6.0 Hz, 1 H), 4.55 (quin, J = 6.3 Hz, 1 H), 1.40 (d, J = 6.0 Hz, 6 H), 1.40 (d, J = 6.0 Hz, 6 H).

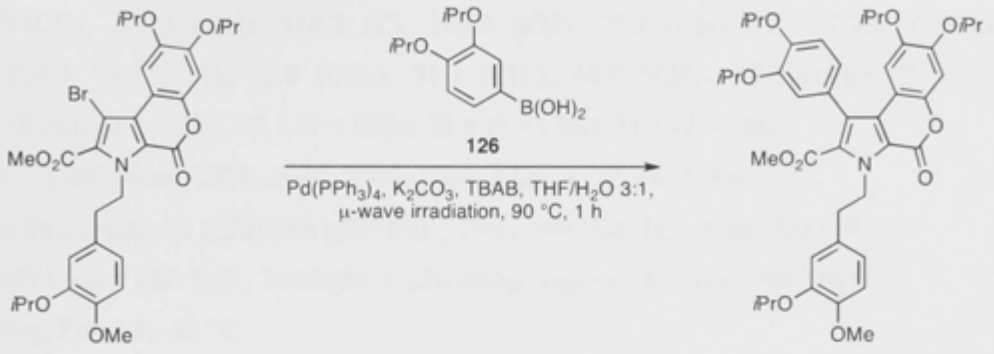
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (C), 148.1 (C), 130.6 (CH), 125.8 (CH), 115.7 (CH), 72.9 (CH), 71.3 (CH), 22.3 (2 × CH_3), 22.1 (2 × CH_2) (signal due to sp^2-hybridized carbon bearing boron not observed).

IR ν_{max} (NaCl)/cm^{-1} 3493, 2976, 2932, 1598, 1412, 1341, 1263, 1109, 948.

Melting Point 44-47 °C.

Satisfactory mass spectral data could not be obtained on this compound.

Methyl 1-(3,4-diisopropoxyphenyl)-7,8-diisopropoxy-3-(3-isopropoxy-4-methoxyphenethyl)-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylate (143)



142 **143**

A magnetically stirred solution of pyrrole **142** (63 mg, 0.10 mmol) in THF/H_2O (2.3 mL of 3:1 v/v mixture) was treated with potassium carbonate (0.055 g, 0.40 mmol), TBAB (6 mg, 20 mol %) and boronic acid **126** (43 mg, 0.18 mmol). The resulting mixture was flushed with nitrogen, then $Pd(PPh_3)_4$ (12 mg, 10 mol %) was added and the reaction vessel again flushed with nitrogen then sealed. The reaction mixture was subjected to microwave irradiation (150 W, 90 °C, 1 min ramp time) for 1.5 h then cooled and diluted with H_2O (20 mL) before being extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → 1:1 pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v pentane/diethyl ether) furnished the *title compound **143*** (50 mg, 67%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.1 Hz, 1 H), 6.90 (s, 1 H), 6.88-6.80 (complex m, 3 H), 6.79 (m, 2 H), 6.61 (s, 1 H), 5.10 (t, *J* = 7.2 Hz, 2 H), 4.60-4.40 (complex m, 4 H), 3.94 (quin, *J* = 6.0 Hz, 1 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 3.11-3.02 (complex m, 2 H), 1.40 (d, *J* = 6.0 Hz, 3 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.34 (d, *J* = 5.7 Hz, 3 H), 1.34 (d, *J* = 5.7 Hz, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.13 (d, *J* = 5.7 Hz, 3 H), 1.12 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (C), 155.2 (C), 149.1 (C), 149.0 (C), 148.9 (C), 148.7 (C), 147.2 (C), 146.2 (C), 145.4 (C), 130.5 (CH), 129.4 (C), 127.8 (C), 126.9 (C), 124.4 (C), 123.2 (CH), 121.5 (CH), 119.8 (CH), 117.7 (CH), 117.5 (C), 116.5 (C), 111.9 (CH), 110.5 (CH), 110.3 (C), 105.2 (CH), 72.2 (CH), 72.1 (CH), 72.1 (CH), 72.0 (CH), 71.2 (CH), 56.0 (CH_3), 51.7 (CH_3), 48.6 (CH_2), 37.8 (CH_2), 22.4 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 22.1 (3 × CH_3), 21.9 (2 × CH_3), 21.9 (2 × CH_3).

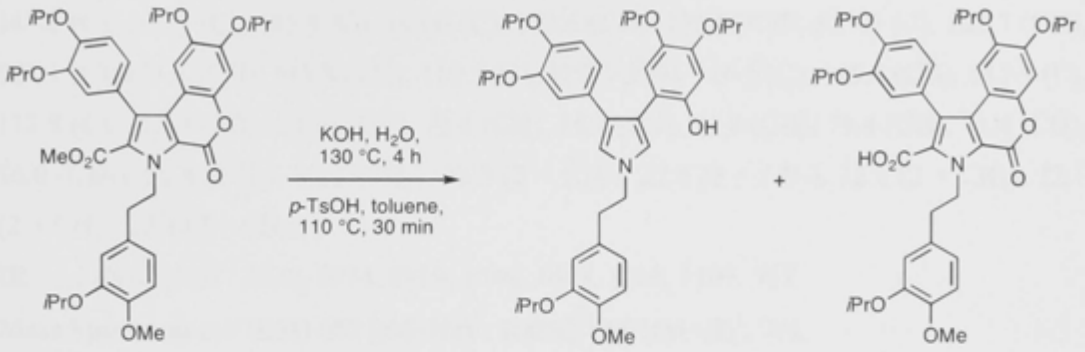
IR ν_{max} (NaCl)/cm^{-1} 2976, 2933, 1730, 1264, 1226, 1110, 1017, 936.

Mass Spectrum *m/z* (ESI) 766 [$(M+Na)^+$, 78%], 744 [$(M+H)^+$, 100], 702 (18).

HRMS Found: $(M+Na)^+$, 766.3568. $C_{43}H_{53}NO_{10}$ requires $(M+Na)^+$, 766.3567.

Melting Point 36-42 °C.

1-(3,4-Diisopropoxyphenyl)-7,8-diisopropoxy-3-(3-isopropoxy-4-methoxyphenethyl)-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylic acid (124)



143 144 124

Following the procedure detailed by Steglich *et al.*,[9] a finely ground sample of compound **143** (243 mg, 0.33 mmol) was suspended in a freshly prepared, degassed solution of KOH (8.1 g, 0.144 mol) in water (12.5 mL). The resulting mixture was heated at 130 °C for 4 h and the methanol so formed was removed by continuous distillation. The reaction mixture was cooled to 0 °C, acidified by the dropwise addition of HCl (37% w/v aqueous solution), and then extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a deep-yellow oil. The residue thus obtained was dissolved in toluene (43 mL) and the resulting solution treated with *p*-toluenesulfonic acid monohydrate (24 mg) and 4 Å molecular sieves (351 mg) then heated at reflux for 0.5 h. The cooled reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:1 v/v pentane/diethyl ether + 1% acetic acid → 1:1 pentane/diethyl ether + 1% acetic acid gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:1 v/v pentane/diethyl ether) afforded compound **144** (34 mg, 16%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84-6.74 (complex m, 4 H), 6.71 (s, 1 H), 6.67 (s, 1 H), 6.66 (dd, *J* = 8.4 and 1.5 Hz, 1 H), 6.59 (d, *J* = 1.8 Hz, 1 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.48 (s, 1 H), 5.06 (s, 1 H), 4.45 (quin, *J* = 6.0 Hz, 1 H), 4.42 (quin, *J* = 6.0 Hz, 1 H), 4.37 (quin, *J* = 5.7 Hz, 1 H), 4.24-4.12 (complex m, 1 H), 4.09 (t, *J* = 6.9 Hz, 2 H), 3.84 (s, 3 H), 3.01 (t,

J = 6.9 Hz, 2 H), 1.34 (d, J = 6.0 Hz, 6 H), 1.29 (d, J = 6.0 Hz, 6 H), 1.29 (d, J = 6.3 Hz, 6 H), 1.20 (d, J = 6.3 Hz, 6 H), 1.17 (d, J = 5.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8 (C), 149.3 (C), 149.0 (C), 148.7 (C), 147.2 (C), 147.2 (C), 141.8 (C), 145.8 (C), 145.6 (C), 130.6 (CH), 128.9 (CH), 123.5 (C), 122.7 (CH), 121.1 (C), 121.1 (CH), 119.8 (CH), 119.5 (C), 118.7 (CH), 116.5 (C), 116.4 (CH), 115.9 (C), 113.8 (C), 112.0 (CH), 103.8 (CH), 73.5 (CH), 72.4 (CH), 71.6 (CH), 71.4 (CH), 71.4 (CH), 56.0 (CH_3), 51.8 (CH_2), 37.7 (CH_2), 22.3 (2 × CH_3), 22.2 (2 × CH_3), 22.2 (2 × CH_3), 22.1 (2 × CH_3), 22.1 (2 × CH_3).

IR ν_{max} (NaCl)/cm^{-1} 3436, 2974, 2929, 1540, 1499, 1261, 1109, 957.

Mass Spectrum *m/z* (ESI) 682 [$(M+Na)^+$, 100%], 660 [$(M+H)^+$, 76].

HRMS Found: $(M+Na)^+$, 682.3719. $C_{40}H_{53}NO_7$ requires $(M+Na)^+$, 682.3720.

Concentration of fraction B (R_f = 0.1 in 1:1 v/v pentane/diethyl ether) afforded *compound **124*** (118 mg, 49%) as a pale-brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (broad s, 1 H), 6.99 (d, J = 8.1 Hz, 1 H), 6.94-6.82 (complex m, 4 H), 6.80-6.70 (complex m, 2 H), 6.55 (s, 1 H), 5.14 (t, J = 8.1 Hz, 2 H), 4.60-4.38 (complex m, 4 H), 3.93 (quin, J = 5.7 Hz, 1 H), 3.79 (s, 3 H), 3.06 (d, J = 6.9 Hz, 2 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.33 (d, J = 6.3 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H), 1.13 (d, J = 5.7 Hz, 3 H), 1.12 (d, J = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (C), 155.2 (C), 149.1 (C), 149.1 (C), 149.0 (C), 148.9 (C), 147.2 (C), 146.1 (C), 145.4 (C), 130.3 (C), 128.0 (C), 127.1 (C), 126.9 (C), 126.0 (C), 123.1 (CH), 121.5 (CH), 119.9 (CH), 118.4 (C), 117.3 (CH), 116.6 (CH), 112.1 (CH), 110.4 (C), 110.1 (CH), 105.1, 72.2 (CH), 72.0 (3 × CH), 71.3 (CH), 56.0 (CH_3), 48.8 (CH_2), 37.8 (CH_2), 22.4 (CH_3), 22.1 (2 × CH_3), 22.1 (3 × CH_3), 21.9 (2 × CH_3), 21.9 (CH_3), 21.8 (CH_3).

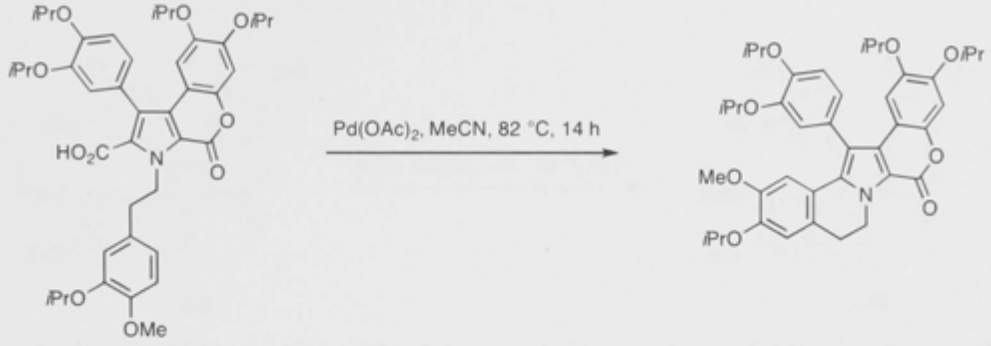
IR ν_{max} (NaCl)/cm^{-1} 3292, 2975, 2926, 1729, 1261, 1109, 974.

Mass Spectrum *m/z* (EI, 70 eV) 729 ($M^{+\cdot}$, 74%), 685 (100), 369 (72), 325 (87), 151 (66).

HRMS Found: $M^{+\cdot}$, 729.3528. $C_{42}H_{51}NO_{10}$ requires $M^{+\cdot}$, 729.3513.

Melting Point no melting point, decomposition above 170 °C.

Lamellarin S Perisopropyl Ether (123)



124 **123**

Following the procedure detailed by Iwao *et al.*,[8] a magnetically stirred solution of pyrrole **124** (40 mg, 0.06 mmol) and palladium acetate (14 mg, 0.006 mmol) in acetonitrile (5 mL) was heated to 82 °C for 14 h. After cooling the reaction mixture to 18 °C, it was subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether + 1% triethyl amine → 1:1 pentane/diethyl ether +1% triethyl amine gradient elution) and concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v pentane/diethyl ether) afforded the *title compound **123*** (21 mg, 56%) as a yellow, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 1 H), 7.03 (s, 1 H), 7.01 (d, *J* = 4.8 Hz, 1 H), 6.92 (s, 1 H), 6.76 (s, 1 H), 6.72 (s, 1 H), 6.71 (s, 1 H), 4.90-4.66 (complex m, 2 H), 4.60-4.38 (complex m, 4 H), 3.97 (sept, *J* = 5.7 Hz, 1 H), 3.34 (s, 3 H), 3.08 (t, *J* = 6.6 Hz, 2 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 1.39 (d, *J* = 6.3 Hz, 3 H), 1.37 (d, *J* = 6.6 Hz, 6 H), 1.34 (d, *J* = 6.3 Hz, 6 H), 1.31 (d, *J* = 5.4 Hz, 3 H), 1.29 (d, *J* = 5.7 Hz, 3 H), 1.14 (d, *J* = 5.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (C), 150.2 (C), 148.8 (C), 148.7 (C), 148.6 (C), 147.2 (C), 146.4 (C), 145.2 (C), 136.0 (C), 129.2 (CH), 128.2 (C), 126.3 (C), 123.8 (CH), 120.2 (C), 119.5 (1 × CH, 1 × C), 115.0 (C), 114.6 (C), 113.6 (C), 111.1 (C), 110.8 (CH), 109.1 (CH), 105.3 (CH), 72.8 (CH), 72.2 (CH), 72.1 (CH), 71.9 (CH), 71.3 (CH), 55.1 (CH_3), 42.4 (CH_2), 28.7 (CH_2), 22.2 (2 × CH_3), 22.2 (2 × CH_3), 22.1 (2 × CH_3), 22.0 (2 × CH_3), 22.0 (2 × CH_3).

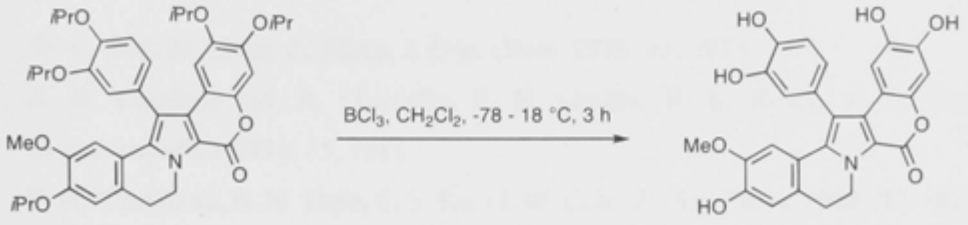
IR ν_{max} (NaCl)/cm^{-1} 2975, 2928, 1710, 1109.

Mass Spectrum *m/z* (EI) 683 ($M^{+\cdot}$, 100%), 642 (18), 533 (25), 473 (18), 236 (18).

HRMS Found: $(M+Na)^+$, 706.3362. $C_{41}H_{49}NO_8$ requires $(M+Na)^+$, 706.3356.

Melting Point 169-178 °C.

Lamellarin S (120)



123 120

Boron trichloride (175 μL of a 1 M solution in dichloromethane, 0.175 mmol) was added, dropwise over 5 min, to a magnetically stirred solution of compound **123** (12 mg, 0.0175 mmol) in dichloromethane (3 mL) maintained at −78 °C under nitrogen. Stirring was continued at this temperature for 0.66 h then the cooling bath was removed and the reaction mixture allowed to warm to 18 °C over 0.5 h. Stirring was continued at 18 °C for 2 h then the reaction mixture was quenched with methanol (10 mL) and concentrated under reduced pressure. The resulting yellow solid was subjected to flash chromatography (silica, $CHCl_3$ → 9:3 v/v $CHCl_3$/ethanol gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 9:3 v/v $CHCl_3$/ethanol) afforded lamellarin S (**120**) (8 mg, 97%) as a pale-brown solid.

^{1}H NMR (500 MHz, CD_3OD) δ 7.00 (d, J = 8.0 Hz, 1 H), 6.88 (m, 1 H), 6.84 (s, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.76 (s, 1 H), 6.71 (s, 1 H), 6.64 (s, 1 H), 4.72-4.60 (complex m, 2 H), 3.40 (s, 3 H), 3.02 (m, 2 H).

^{13}C NMR (125 MHz, CD_3OD) δ (125 MHz, CD_3OD) 157.7 (C), 148.1 (C), 147.5 (C), 147.4 (C), 147.3 (C), 146.8 (C), 146.7 (C), 143.4 (C), 138.6 (C), 130.0 (C), 128.7 (C), 128.1 (C), 123.7 (CH), 120.2 (C), 119.1 (C), 117.5 (CH), 116.5 (C), 115.8 (CH), 113.8 (CH), 111.3 (C), 110.4 (CH), 109.9 (CH), 104.2 (CH), 55.6 (CH_3), 43.6 (CH_2), 29.3 (CH_2).

IR ν_{max} (KBr)/cm^{-1} 3422, 2924, 2853, 1667, 1279, 1156, 1040.

Mass Spectrum *m/z* (ESI) 496 [$(M+Na)^+$, 78%], 474 [$(M+H)^+$, 100], 305 (21), 180 (18), 123 (18).

HRMS Found: $(M+Na)^+$, 496.1007. $C_{26}H_{19}NO_8$ requires $(M+Na)^+$, 496.1008.

Melting Point >390 °C. (lit.[15] m.p. = >300 °C).

HPLC R_t = 8.05 min (Agilent Zorbax C_{18} 5 μm, 4.6 x 150 mm column, 1 mL/min gradient elution from 1:9 v/v H_2O/acetonitrile → acetonitrile over 15 min with a constant 0.01% v/v TFA/acetonitrile as modifier, monitoring by DAD at 276 nm).

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Appendices

6.1 Crystallographic Studies Associated with Compounds in Chapter 2 ____ 161

1-Bromo-3-(3,4-dimethoxyphenethyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (**44**) __ 161

3-(3,4-Dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-*b*]-pyrrol-4(3*H*)-one (**34**) ____ 166

tert-Butyl 4-oxochromeno[3,4-*b*]pyrrole-3(4*H*)-carboxylate (**51**) ____ 171

6.2 Crystallographic Studies Associated with Compounds in Chapter 3 ____ 176

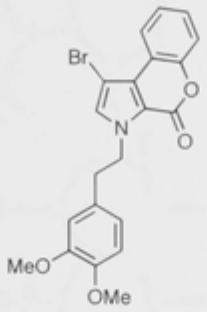
1-Bromo-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**85**) ____ 176

Dimethyl 3,4-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2,5-dicarboxylate (**98**) ____ 181

Dimethyl 3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (**101**) ____ 187

6.1 Crystallographic Studies Associated with Compounds in Chapter 2

1-Bromo-3-(3,4-dimethoxyphenethyl)chromeno[3,4-*b*]pyrrol-4(3*H*)-one (44)



44

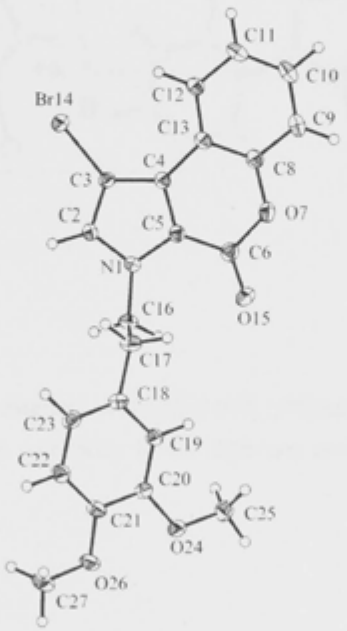


Figure 6.1. Molecular structure of $C_{21}H_{18}BrNO_4$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

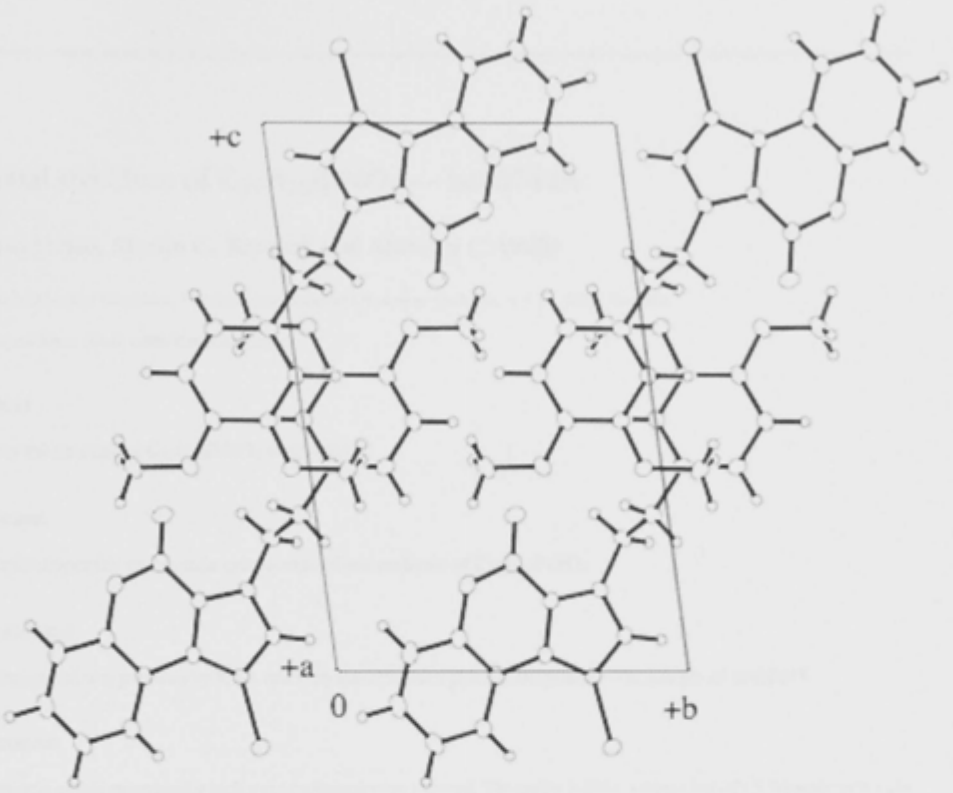


Figure 6.2. Unit cell packing diagram of $C_{21}H_{18}BrNO_4$ projected down the *a* axis. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Crystal structure of $C_{21}H_{18}BrNO_4$ — ban0743A

Katrin Hasse, Martin G. Banwell and Anthony C. Willis

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: **willis@rsc.anu.edu.au**

Abstract

The crystal structure of $C_{21}H_{18}BrNO_4$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{21}H_{18}BrNO_4$.

Experimental

The compound was prepared by KAA and recrystallized from pentane/diethylether. The sample ID is kah215.

Refinement

All crystals of this compound which were examined were twinned. The utility *DIRAX* within *COLLECT* identified the twin components to be related by a 180° rotation about the direct axis 1 0 0. This relationship was also recognized by ROTAX within *CRYSTALS* and enabled the application of a twinning correction during refinement of the structure. Twin elements refined to 0.512 (2):0.488 (2).

Most hydrogen atoms were observed in difference electron density maps prior to their inclusion. All hydrogen atoms were included at calculated positions and ride on the atom to which they are attached during refinement.

The largest peaks in a final difference electron density map are located near the Br atom or its twin-related position.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEPII* (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0743A)

Crystal data

$C_{21}H_{18}BrNO_4$	$\gamma = 93.102\ (3)^\circ$
$M_r = 428.28$	$V = 913.36\ (7)\ Å^3$
Triclinic, $P\overline{1}$	$Z = 2$
$a = 7.3505\ (3)$ Å	Mo $K\alpha$
$b = 8.9299\ (4)$ Å	$\mu = 2.28\ mm^{-1}$
$c = 14.1446\ (7)$ Å	$T = 200$ K
$\alpha = 97.197\ (2)^\circ$	$0.26 \times 0.13 \times 0.06$ mm
$\beta = 96.320\ (3)^\circ$	

Data collection

Nonius KappaCCD diffractometer	4201 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	3120 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.629$, $T_{max} = 0.879$	$R_{int} = 0.051$
16071 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.037$	245 parameters
$wR(F^2) = 0.082$	H-atom parameters not refined
$S = 0.93$	$\Delta\rho_{max} = 0.42$ e Å^{-3}
4201 reflections	$\Delta\rho_{min} = -0.45$ e Å^{-3}

Selected geometric parameters (Å, °)

N1—C2	1.354 (3)	C10—C11	1.386 (4)
N1—C5	1.380 (3)	C11—C12	1.384 (3)
N1—C16	1.468 (3)	C12—C13	1.400 (3)
C2—C3	1.375 (3)	C16—C17	1.519 (4)
C3—C4	1.414 (3)	C17—C18	1.519 (3)
C3—Br14	1.877 (2)	C18—C19	1.400 (3)
C4—C5	1.388 (3)	C18—C23	1.373 (3)
C4—C13	1.452 (3)	C19—C20	1.380 (3)
C5—C6	1.429 (3)	C20—C21	1.407 (3)
C6—O7	1.383 (3)	C20—O24	1.369 (3)
C6—O15	1.209 (3)	C21—C22	1.379 (4)
O7—C8	1.388 (3)	C21—O26	1.370 (3)
C8—C9	1.388 (3)	C22—C23	1.400 (3)
C8—C13	1.390 (3)	O24—C25	1.424 (3)
C9—C10	1.381 (4)	O26—C27	1.432 (3)
C2—N1—C5	108.10 (19)	C10—C11—C12	119.5 (3)
C2—N1—C16	123.3 (2)	C11—C12—C13	121.0 (2)

C5—N1—C16	128.6 (2)	C4—C13—C12	126.2 (2)
N1—C2—C3	109.1 (2)	C4—C13—C8	115.9 (2)
C2—C3—C4	108.0 (2)	C12—C13—C8	117.9 (2)
C2—C3—Br14	122.96 (17)	N1—C16—C17	111.8 (2)
C4—C3—Br14	129.01 (18)	C16—C17—C18	111.7 (2)
C3—C4—C5	105.6 (2)	C17—C18—C19	119.4 (2)
C3—C4—C13	135.4 (2)	C17—C18—C23	121.4 (2)
C5—C4—C13	119.0 (2)	C19—C18—C23	119.2 (2)
C4—C5—N1	109.2 (2)	C18—C19—C20	120.7 (2)
C4—C5—C6	124.7 (2)	C19—C20—C21	119.9 (2)
N1—C5—C6	126.1 (2)	C19—C20—O24	124.8 (2)
C5—C6—O7	113.9 (2)	C21—C20—O24	115.2 (2)
C5—C6—O15	128.4 (2)	C20—C21—C22	119.3 (2)
O7—C6—O15	117.7 (2)	C20—C21—O26	115.3 (2)
C6—O7—C8	123.35 (19)	C22—C21—O26	125.5 (2)
O7—C8—C9	115.3 (2)	C21—C22—C23	120.3 (2)
O7—C8—C13	123.0 (2)	C22—C23—C18	120.6 (2)
C9—C8—C13	121.8 (2)	C20—O24—C25	116.63 (19)
C8—C9—C10	119.0 (3)	C21—O26—C27	116.0 (2)
C9—C10—C11	120.8 (2)		

References

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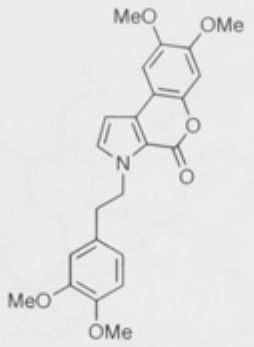
3-(3,4-Dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (34)



34

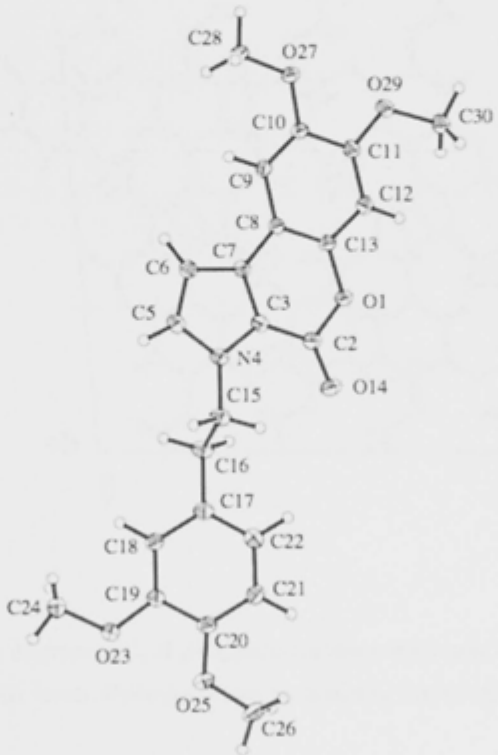


Figure 6.3. Molecular structure of $C_{23}H_{23}NO_6$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

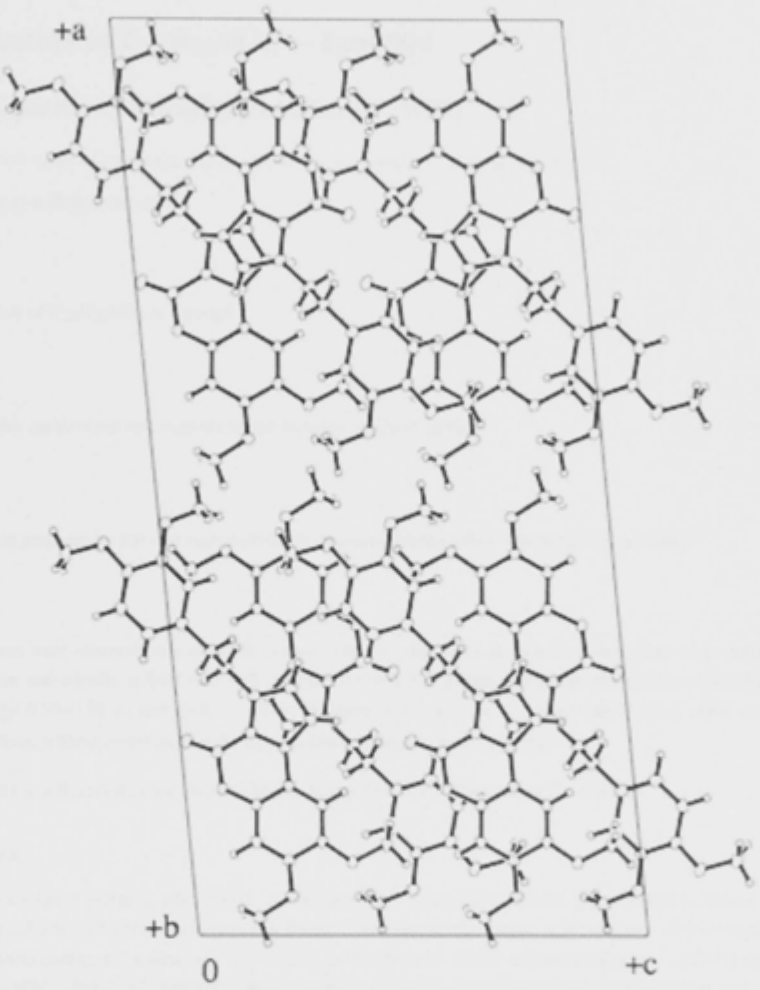


Figure 6.4. Unit cell packing diagram of $C_{23}H_{23}NO_6$ projected down the *b* axis. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Crystal structure of $C_{23}H_{23}NO_6$ — ban0904

Katrin Hasse, Martin G. Banwell and Anthony C. Willis

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: **willis@rsc.anu.edu.au**

Abstract

The crystal structure of $C_{23}H_{23}NO_6$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{23}H_{23}NO_6$.

Experimental

The compound was prepared by KH and recrystallized from pentane/diethylether. The sample ID is kah427.

Refinement

All hydrogen atoms were observed in a difference electron density map prior to their inclusion. They were included at calculated positions and initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2–1.5 times U_{eq} of the parent atom, after which the positions were refined without restraints and the displacement parameters were held fixed.

The major peaks in a final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 1997-2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(ban0904)

Crystal data

$C_{23}H_{23}NO_6$	$V = 3993.39\,(12)$ Å^3
$M_r = 409.44$	$Z = 8$

Monoclinic, $C2/c$	Mo $K\alpha$
a = 33.6193 (7) Å	μ = 0.10 mm^{-1}
b = 7.24830 (10) Å	T = 200 K
c = 16.4673 (3) Å	0.31 × 0.28 × 0.04 mm
β = 95.6376 (12)°	

Data collection

Area diffractometer	4609 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	2895 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.971, T_{max} = 0.997	R_{int} = 0.046
41243 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.035	340 parameters
$wR(F^2)$ = 0.083	Only H-atom coordinates refined
S = 0.79	$\Delta\rho_{max}$ = 0.26 e Å^{-3}
4608 reflections	$\Delta\rho_{min}$ = −0.28 e Å^{-3}

Table 1
Selected geometric parameters (Å, °)

O1—C2	1.3837 (15)	C11—O29	1.3567 (14)
O1—C13	1.3874 (13)	C12—C13	1.3898 (17)
C2—C3	1.4302 (17)	C15—C16	1.5237 (18)
C2—O14	1.2155 (14)	C16—C17	1.5101 (17)
C3—N4	1.3811 (15)	C17—C18	1.3946 (18)
C3—C7	1.3882 (16)	C17—C22	1.3836 (18)
N4—C5	1.3596 (16)	C18—C19	1.3845 (17)
N4—C15	1.4662 (15)	C19—C20	1.3992 (17)
C5—C6	1.3715 (17)	C19—O23	1.3688 (15)
C6—C7	1.4099 (17)	C20—C21	1.3766 (18)
C7—C8	1.4398 (16)	C20—O25	1.3726 (15)
C8—C9	1.4081 (16)	C21—C22	1.3884 (18)
C8—C13	1.3895 (16)	O23—C24	1.4224 (17)
C9—C10	1.3751 (17)	O25—C26	1.4254 (17)
C10—C11	1.4147 (16)	O27—C28	1.4287 (15)
C10—O27	1.3677 (13)	O29—C30	1.4368 (16)
C11—C12	1.3788 (17)		
C2—O1—C13	123.43 (9)	C12—C11—O29	124.83 (11)
O1—C2—C3	113.92 (10)	C11—C12—C13	119.48 (11)
O1—C2—O14	116.92 (11)	C12—C13—C8	121.83 (11)
C3—C2—O14	129.15 (12)	C12—C13—O1	115.51 (10)
C2—C3—N4	127.11 (11)	C8—C13—O1	122.66 (11)
C2—C3—C7	124.54 (11)	N4—C15—C16	113.22 (10)

N4—C3—C7	108.32 (10)	C15—C16—C17	110.32 (10)
C3—N4—C5	107.47 (10)	C16—C17—C18	121.22 (12)
C3—N4—C15	127.84 (10)	C16—C17—C22	120.49 (12)
C5—N4—C15	124.67 (11)	C18—C17—C22	118.27 (12)
N4—C5—C6	110.51 (11)	C17—C18—C19	121.15 (12)
C5—C6—C7	106.30 (11)	C18—C19—C20	119.58 (12)
C6—C7—C3	107.39 (11)	C18—C19—O23	125.80 (11)
C6—C7—C8	133.52 (11)	C20—C19—O23	114.63 (11)
C3—C7—C8	119.06 (11)	C19—C20—C21	119.63 (12)
C7—C8—C9	125.38 (11)	C19—C20—O25	115.12 (11)
C7—C8—C13	116.39 (10)	C21—C20—O25	125.24 (11)
C9—C8—C13	118.22 (11)	C20—C21—C22	120.17 (12)
C8—C9—C10	120.59 (11)	C21—C22—C17	121.18 (13)
C9—C10—C11	120.08 (11)	C19—O23—C24	117.86 (11)
C9—C10—O27	125.17 (11)	C20—O25—C26	116.94 (12)
C11—C10—O27	114.75 (10)	C10—O27—C28	116.80 (10)
C10—C11—C12	119.77 (11)	C11—O29—C30	116.93 (10)
C10—C11—O29	115.40 (10)		

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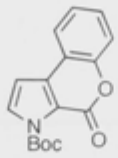
tert-Butyl 4-oxochromeno[3,4-*b*]pyrrole-3(4*H*)-carboxylate (51)



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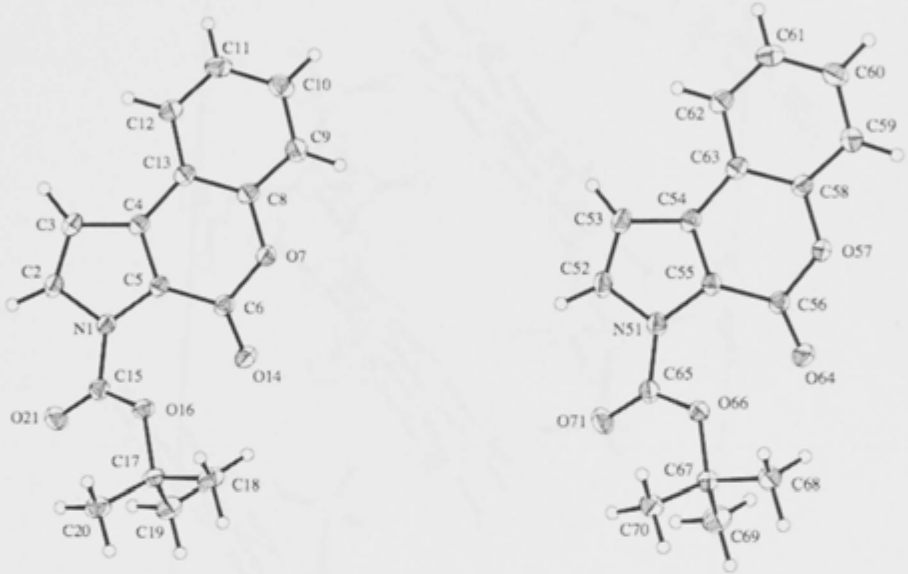

Figure 6.5. Structure of molecule one and two of $C_{16}H_{15}NO_4$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

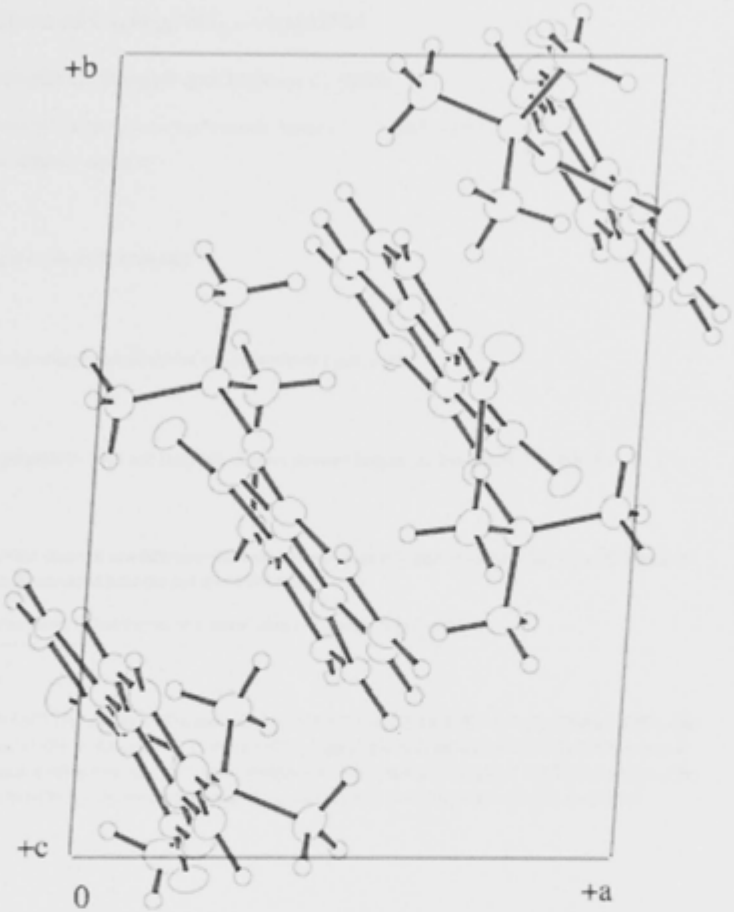

Figure 6.6. Unit cell packing diagram of $C_{16}H_{15}NO_4$ projected down the *c* axis. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Crystal structure of $C_{16}H_{15}NO_4$ — ban0744

Katrin Hasse, Martin G. Banwell and Anthony C. Willis

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: willis@rsc.anu.edu.au

Abstract

The crystal structure of $C_{16}H_{15}NO_4$ is reported.

Comment

The crystallographic asymmetric unit consists of two molecules of $C_{16}H_{15}NO_4$.

Experimental

The compound was prepared by KAA and recrystallized from pentane/diethylether. The sample ID is kah166.

Refinement

All hydrogen atoms were observed in a difference electron density map prior to their inclusion. They were included in the refinement procedure at calculated positions and then refined positionally.

The largest peaks in a final difference electron density map are located along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0744)

Crystal data

$C_{16}H_{15}NO_4$	$\gamma = 81.8995\ (14)^\circ$
$M_r = 285.30$	$V = 1394.80\ (5)$ Å^3
Triclinic, $P\overline{1}$	$Z = 4$
$a = 8.5419\ (2)$ Å	Mo $K\alpha$

b = 13.3119 (2) Å	μ = 0.10 mm^{-1}
c = 13.6091 (3) Å	T = 200 K
α = 67.8584 (13)°	0.40 × 0.36 × 0.21 mm
β = 77.1770 (13)°	

Data collection

Nonius KappaCCD diffractometer	6407 independent reflections
Absorption correction: multi-scan multi-scan from symmetry-related measurements Sortav (Blessing 1995, 1997)	4538 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.921, T_{max} = 0.981	R_{int} = 0.034
33335 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034	469 parameters
$wR(F^2)$ = 0.086	Only H-atom coordinates refined
S = 0.89	$\Delta\rho_{max}$ = 0.27 e Å^{-3}
6392 reflections	$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Selected geometric parameters (Å, °)

N1—C2	1.3872 (13)	N51—C52	1.3864 (14)
N1—C5	1.3937 (13)	N51—C55	1.3975 (14)
N1—C15	1.4193 (14)	N51—C65	1.4170 (14)
C2—C3	1.3544 (16)	C52—C53	1.3530 (17)
C3—C4	1.4247 (15)	C53—C54	1.4234 (15)
C4—C5	1.3821 (14)	C54—C55	1.3775 (15)
C4—C13	1.4382 (15)	C54—C63	1.4420 (15)
C5—C6	1.4427 (15)	C55—C56	1.4453 (14)
C6—O7	1.3873 (13)	C56—O57	1.3864 (13)
C6—O14	1.2047 (13)	C56—O64	1.2038 (13)
O7—C8	1.3811 (13)	O57—C58	1.3815 (13)
C8—C9	1.3847 (16)	C58—C59	1.3852 (16)
C8—C13	1.4007 (15)	C58—C63	1.3933 (15)
C9—C10	1.3839 (17)	C59—C60	1.3756 (18)
C10—C11	1.3882 (18)	C60—C61	1.3882 (19)
C11—C12	1.3783 (17)	C61—C62	1.3775 (18)
C12—C13	1.4005 (15)	C62—C63	1.3993 (16)
C15—O16	1.3153 (13)	C65—O66	1.3138 (13)
C15—O21	1.1972 (13)	C65—O71	1.1996 (13)
O16—C17	1.4966 (12)	O66—C67	1.4810 (13)
C17—C18	1.5166 (17)	C67—C68	1.5135 (17)
C17—C19	1.5108 (17)	C67—C69	1.5102 (18)
C17—C20	1.5143 (17)	C67—C70	1.5151 (16)
C2—N1—C5	107.50 (9)	C52—N51—C55	107.10 (9)

C2—N1—C15	121.16 (9)	C52—N51—C65	120.64 (9)
C5—N1—C15	130.64 (9)	C55—N51—C65	130.61 (9)
N1—C2—C3	109.87 (10)	N51—C52—C53	110.30 (10)
C2—C3—C4	107.01 (10)	C52—C53—C54	106.65 (11)
C3—C4—C5	107.76 (10)	C53—C54—C55	108.11 (10)
C3—C4—C13	132.59 (10)	C53—C54—C63	131.69 (10)
C5—C4—C13	119.63 (10)	C55—C54—C63	120.19 (9)
N1—C5—C4	107.85 (9)	N51—C55—C54	107.83 (9)
N1—C5—C6	127.53 (10)	N51—C55—C56	128.03 (10)
C4—C5—C6	123.51 (10)	C54—C55—C56	123.13 (10)
C5—C6—O7	113.69 (9)	C55—C56—O57	113.69 (9)
C5—C6—O14	129.16 (10)	C55—C56—O64	129.84 (10)
O7—C6—O14	117.13 (10)	O57—C56—O64	116.42 (9)
C6—O7—C8	123.94 (8)	C56—O57—C58	124.15 (8)
O7—C8—C9	116.25 (10)	O57—C58—C59	116.29 (10)
O7—C8—C13	121.99 (10)	O57—C58—C63	122.03 (10)
C9—C8—C13	121.75 (11)	C59—C58—C63	121.67 (11)
C8—C9—C10	118.82 (12)	C58—C59—C60	118.84 (12)
C9—C10—C11	120.48 (12)	C59—C60—C61	120.70 (12)
C10—C11—C12	120.57 (12)	C60—C61—C62	120.29 (12)
C11—C12—C13	120.21 (11)	C61—C62—C63	120.14 (12)
C4—C13—C8	116.42 (10)	C54—C63—C62	125.46 (10)
C4—C13—C12	125.40 (10)	C54—C63—C58	116.16 (10)
C8—C13—C12	118.17 (10)	C62—C63—C58	118.34 (10)
N1—C15—O16	110.19 (9)	N51—C65—O66	109.51 (9)
N1—C15—O21	121.14 (10)	N51—C65—O71	121.51 (10)
O16—C15—O21	128.59 (10)	O66—C65—O71	128.95 (11)
C15—O16—C17	119.69 (8)	C65—O66—C67	121.53 (8)
O16—C17—C18	101.78 (9)	O66—C67—C68	100.87 (9)
O16—C17—C19	108.80 (9)	O66—C67—C69	109.14 (10)
C18—C17—C19	111.26 (11)	C68—C67—C69	111.30 (11)
O16—C17—C20	110.03 (9)	O66—C67—C70	110.28 (9)
C18—C17—C20	110.83 (11)	C68—C67—C70	111.21 (11)
C19—C17—C20	113.49 (11)	C69—C67—C70	113.33 (11)

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Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487–1487.

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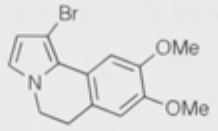
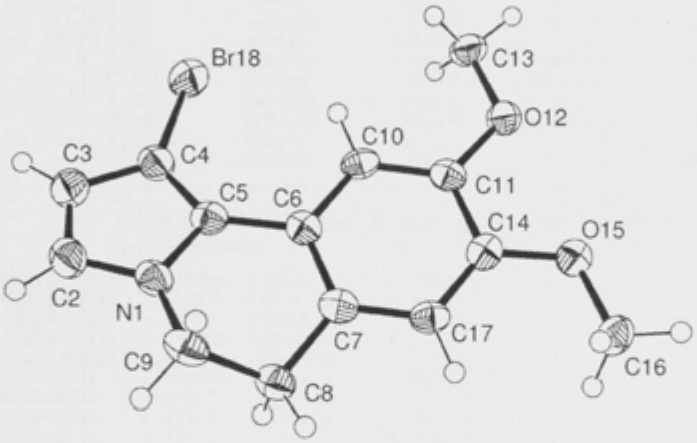
6.2 Crystallographic Studies Associated with Compounds in Chapter 3

1-Bromo-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (85)



85

X-ray structure analysis for Katrin Hasse (Prof. Martin G. Banwell)
by Dr. Jörg Kagler



ORTEP plot with ellipsoids at the 50% level. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were refined isotropically in idealized positions (riding model). The two highest residual electron density peaks were found in close proximity to the bromine atom, further peaks are located on bond axes. There is no indication of disorder in the structure.

Table 1. Crystal data and structure refinement for KH00101.

Identification code	kh00101
Empirical formula	C14 H14 Br N O2
Formula weight	308.17
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 11.0145(7) A alpha = 90 deg.
	b = 13.8140(8) A beta = 104.029(3) deg.
	c = 8.4559(5) A gamma = 90 deg.
Volume	1248.23(13) A^3
Z, Calculated density	4, 1.640 Mg/m^3
Absorption coefficient	3.286 mm^-1
F(000)	624
Crystal size	0.15 x 0.08 x 0.04 mm
Theta range for data collection	2.89 to 25.00 deg.
Limiting indices	-13<=h<=13, -16<=k<=16, -10<=l<=10
Reflections collected / unique	11162 / 2183 [R(int) = 0.0577]
Completeness to theta = 25.00	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.880 and 0.683
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2183 / 0 / 165
Goodness-of-fit on F^2	1.119
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1598
R indices (all data)	R1 = 0.0745, wR2 = 0.1685
Largest diff. peak and hole	0.805 and -0.707 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for KH00101.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(18)	78(1)	246(1)	2280(1)	47(1)
O(15)	5629(4)	344(3)	8454(4)	32(1)
O(12)	3541(3)	1302(3)	7378(4)	32(1)
N(1)	2009(4)	-2260(3)	2997(6)	33(1)
C(2)	1019(6)	-2525(4)	1744(7)	39(1)
C(3)	251(6)	-1760(5)	1335(8)	42(1)
C(4)	768(5)	-990(4)	2381(7)	35(1)
C(5)	1873(5)	-1309(4)	3415(6)	30(1)
C(6)	2846(5)	-875(4)	4727(6)	28(1)
C(7)	3979(5)	-1360(4)	5271(6)	30(1)
C(8)	4188(5)	-2310(4)	4455(7)	34(1)
C(9)	2985(6)	-2880(4)	3947(7)	35(1)
C(10)	2679(5)	18(4)	5442(7)	29(1)
C(11)	3624(5)	418(4)	6659(6)	28(1)
C(13)	2457(5)	1864(4)	6717(8)	38(1)
C(14)	4755(5)	-90(4)	7221(6)	29(1)
C(16)	6719(5)	-230(4)	9137(7)	36(1)
C(17)	4911(5)	-971(4)	6519(6)	30(1)

Table 3. Bond lengths [A] and angles [deg] for KH00101.

Br(18)-C(4)	1.862(6)	C(4)-C(5)	1.387(8)
O(15)-C(14)	1.374(7)	C(5)-C(6)	1.471(8)
O(15)-C(16)	1.437(7)	C(6)-C(7)	1.392(8)
O(12)-C(11)	1.377(6)	C(6)-C(10)	1.406(8)
O(12)-C(13)	1.421(7)	C(7)-C(17)	1.390(8)
N(1)-C(2)	1.373(8)	C(7)-C(8)	1.526(7)
N(1)-C(5)	1.379(7)	C(8)-C(9)	1.511(8)
N(1)-C(9)	1.454(8)	C(10)-C(11)	1.389(8)
C(2)-C(3)	1.346(9)	C(11)-C(14)	1.408(8)
C(3)-C(4)	1.412(8)	C(14)-C(17)	1.382(8)

C(14)-O(15)-C(16)	115.4(4)	C(10)-C(6)-C(5)	122.3(5)
C(11)-O(12)-C(13)	116.8(4)	C(17)-C(7)-C(6)	120.1(5)
C(2)-N(1)-C(5)	109.7(5)	C(17)-C(7)-C(8)	120.8(5)
C(2)-N(1)-C(9)	127.7(5)	C(6)-C(7)-C(8)	119.1(5)
C(5)-N(1)-C(9)	122.1(5)	C(9)-C(8)-C(7)	111.0(4)
C(3)-C(2)-N(1)	108.7(5)	N(1)-C(9)-C(8)	109.3(4)
C(2)-C(3)-C(4)	107.4(6)	C(11)-C(10)-C(6)	121.0(5)
C(5)-C(4)-C(3)	108.3(5)	O(12)-C(11)-C(10)	124.2(5)
C(5)-C(4)-Br(18)	127.3(4)	O(12)-C(11)-C(14)	116.1(5)
C(3)-C(4)-Br(18)	124.3(5)	C(10)-C(11)-C(14)	119.6(5)
N(1)-C(5)-C(4)	105.9(5)	O(15)-C(14)-C(17)	124.9(5)
N(1)-C(5)-C(6)	118.5(5)	O(15)-C(14)-C(11)	116.0(5)
C(4)-C(5)-C(6)	135.6(5)	C(17)-C(14)-C(11)	119.0(5)
C(7)-C(6)-C(10)	118.8(5)	C(14)-C(17)-C(7)	121.4(5)
C(7)-C(6)-C(5)	119.0(5)		

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for KH00101. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(18)	37(1)	48(1)	53(1)	-3(1)	6(1)	5(1)
O(15)	31(2)	33(2)	31(2)	2(2)	7(2)	-1(2)
O(12)	30(2)	29(2)	36(2)	-2(2)	8(2)	-1(2)
N(1)	36(3)	31(3)	36(3)	-5(2)	17(2)	-4(2)
C(2)	40(3)	36(3)	46(3)	-8(3)	19(3)	-12(3)
C(3)	36(3)	47(4)	44(3)	-7(3)	15(3)	-7(3)
C(4)	36(3)	34(3)	38(3)	-3(2)	15(2)	-4(2)
C(5)	30(3)	30(3)	33(3)	2(2)	15(2)	-2(2)
C(6)	32(3)	27(3)	28(3)	2(2)	12(2)	-2(2)
C(7)	35(3)	30(3)	29(3)	5(2)	15(2)	1(2)
C(8)	37(3)	32(3)	36(3)	-2(2)	15(2)	1(2)
C(9)	47(3)	27(3)	39(3)	1(2)	23(3)	2(2)
C(10)	25(3)	32(3)	33(3)	7(2)	13(2)	2(2)
C(11)	32(3)	29(3)	28(3)	3(2)	15(2)	-1(2)
C(13)	28(3)	32(3)	53(4)	-7(3)	9(2)	2(2)
C(14)	28(3)	32(3)	26(3)	6(2)	9(2)	-4(2)
C(16)	32(3)	32(3)	38(3)	3(2)	0(2)	3(2)
C(17)	30(3)	33(3)	29(3)	6(2)	12(2)	5(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for KH00101.

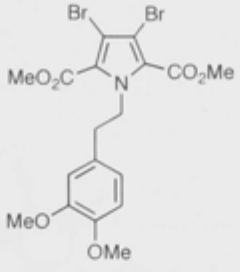
	x	y	z	U(eq)
H(2)	896	-3146	1248	47
H(3)	-499	-1741	497	50
H(8A)	4512	-2171	3484	41
H(8B)	4822	-2701	5221	41
H(9A)	3111	-3446	3286	42
H(9B)	2734	-3119	4925	42
H(10)	1907	353	5087	35
H(13A)	2415	2008	5570	57
H(13B)	2498	2472	7327	57
H(13C)	1710	1502	6797	57
H(16A)	6461	-847	9527	53
H(16B)	7259	120	10051	53
H(16C)	7179	-353	8301	53
H(17)	5671	-1317	6899	36

Table 6. Torsion angles [deg] for KH00101.

C(5)-N(1)-C(2)-C(3)	0.5(6)
C(9)-N(1)-C(2)-C(3)	172.3(5)
N(1)-C(2)-C(3)-C(4)	-0.8(6)
C(2)-C(3)-C(4)-C(5)	0.8(7)
C(2)-C(3)-C(4)-Br(18)	178.4(4)
C(2)-N(1)-C(5)-C(4)	-0.1(6)
C(9)-N(1)-C(5)-C(4)	-172.4(4)
C(2)-N(1)-C(5)-C(6)	-179.3(4)
C(9)-N(1)-C(5)-C(6)	8.4(7)
C(3)-C(4)-C(5)-N(1)	-0.4(6)
Br(18)-C(4)-C(5)-N(1)	-178.0(4)
C(3)-C(4)-C(5)-C(6)	178.7(5)
Br(18)-C(4)-C(5)-C(6)	1.1(9)
N(1)-C(5)-C(6)-C(7)	13.0(7)
C(4)-C(5)-C(6)-C(7)	-166.0(6)
N(1)-C(5)-C(6)-C(10)	-167.8(5)
C(4)-C(5)-C(6)-C(10)	13.2(9)
C(10)-C(6)-C(7)-C(17)	1.2(7)
C(5)-C(6)-C(7)-C(17)	-179.5(5)
C(10)-C(6)-C(7)-C(8)	-177.5(5)
C(5)-C(6)-C(7)-C(8)	1.8(7)
C(17)-C(7)-C(8)-C(9)	146.6(5)
C(6)-C(7)-C(8)-C(9)	-34.7(7)
C(2)-N(1)-C(9)-C(8)	148.1(5)
C(5)-N(1)-C(9)-C(8)	-41.1(6)
C(7)-C(8)-C(9)-N(1)	51.6(6)
C(7)-C(6)-C(10)-C(11)	0.5(7)
C(5)-C(6)-C(10)-C(11)	-178.8(5)
C(13)-O(12)-C(11)-C(10)	-5.7(7)
C(13)-O(12)-C(11)-C(14)	174.1(4)
C(6)-C(10)-C(11)-O(12)	178.0(4)
C(6)-C(10)-C(11)-C(14)	-1.8(7)
C(16)-O(15)-C(14)-C(17)	-6.4(7)
C(16)-O(15)-C(14)-C(11)	173.4(4)
O(12)-C(11)-C(14)-O(15)	1.8(6)
C(10)-C(11)-C(14)-O(15)	-178.4(4)
O(12)-C(11)-C(14)-C(17)	-178.4(4)
C(10)-C(11)-C(14)-C(17)	1.4(7)
O(15)-C(14)-C(17)-C(7)	-179.9(5)
C(11)-C(14)-C(17)-C(7)	0.3(7)
C(6)-C(7)-C(17)-C(14)	-1.7(7)
C(8)-C(7)-C(17)-C(14)	177.1(5)

```
Least-squares planes (x,y,z in crystal coordinates) and deviations from them
 (* indicates atom used to define plane)

 - 6.1426 (0.0190) x - 6.4963 (0.0245) y + 6.7544 (0.0101) z = 2.0106 (0.0112)

 *    0.0030 (0.0035)  C6
 *   -0.0104 (0.0034)  C7
 *    0.0078 (0.0035)  C10
 *   -0.0112 (0.0035)  C11
 *    0.0037 (0.0035)  C14
 *    0.0070 (0.0035)  C17
     -0.0483 (0.0068)  O12
      0.0186 (0.0070)  O15
     -0.0044 (0.0078)  C5
     -0.0735 (0.0082)  C8

 Rms deviation of fitted atoms =   0.0078


 - 7.6058 (0.0219) x - 4.0826 (0.0359) y + 6.8313 (0.0138) z = 1.4436 (0.0085)

 Angle to previous plane (with approximate esd) = 12.68 ( 0.32 )

 *   -0.0016 (0.0031)  N1
 *    0.0038 (0.0034)  C2
 *   -0.0044 (0.0035)  C3
 *    0.0033 (0.0034)  C4
 *   -0.0011 (0.0032)  C5
      0.1579 (0.0088)  C9
     -0.0214 (0.0087)  C6
     -0.0458 (0.0088)  Br18

 Rms deviation of fitted atoms =   0.0031


 - 5.9363 (0.0199) x - 4.2226 (0.0282) y + 7.5440 (0.0079) z = 2.1244 (0.0095)

 Angle to previous plane (with approximate esd) = 11.28 ( 0.31 )

 *   -0.1019 (0.0034)  N1
 *   -0.1075 (0.0035)  C5
 *    0.1221 (0.0035)  C6
 *    0.0648 (0.0035)  C7
 *   -0.2745 (0.0038)  C8
 *    0.2970 (0.0037)  C9

 Rms deviation of fitted atoms =   0.1846


 - 6.3429 (0.0290) x - 4.9727 (0.0460) y + 7.2021 (0.0092) z = 1.9786 (0.0136)

 Angle to previous plane (with approximate esd) =  4.76 ( 0.34 )

 *    0.0294 (0.0016)  N1
 *   -0.0564 (0.0030)  C5
 *    0.0563 (0.0030)  C6
 *   -0.0293 (0.0016)  C7
     -0.2779 (0.0096)  C8
      0.4026 (0.0092)  C9

 Rms deviation of fitted atoms =   0.0449
```

Dimethyl 3,4-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2,5-dicarboxylate (98)



98

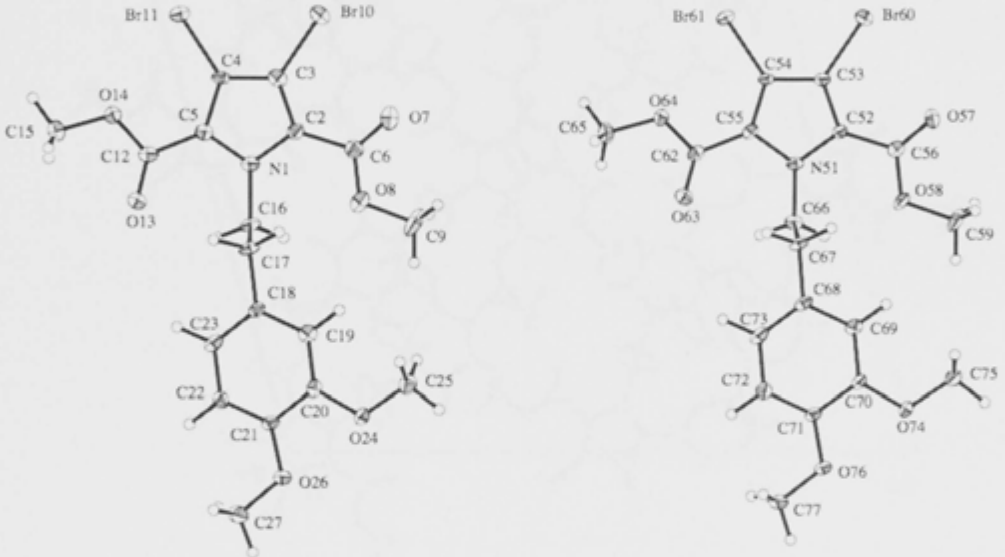


Figure 6.7. Structure of molecule one and molecule two of $C_{18}H_{19}Br_2NO_6$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

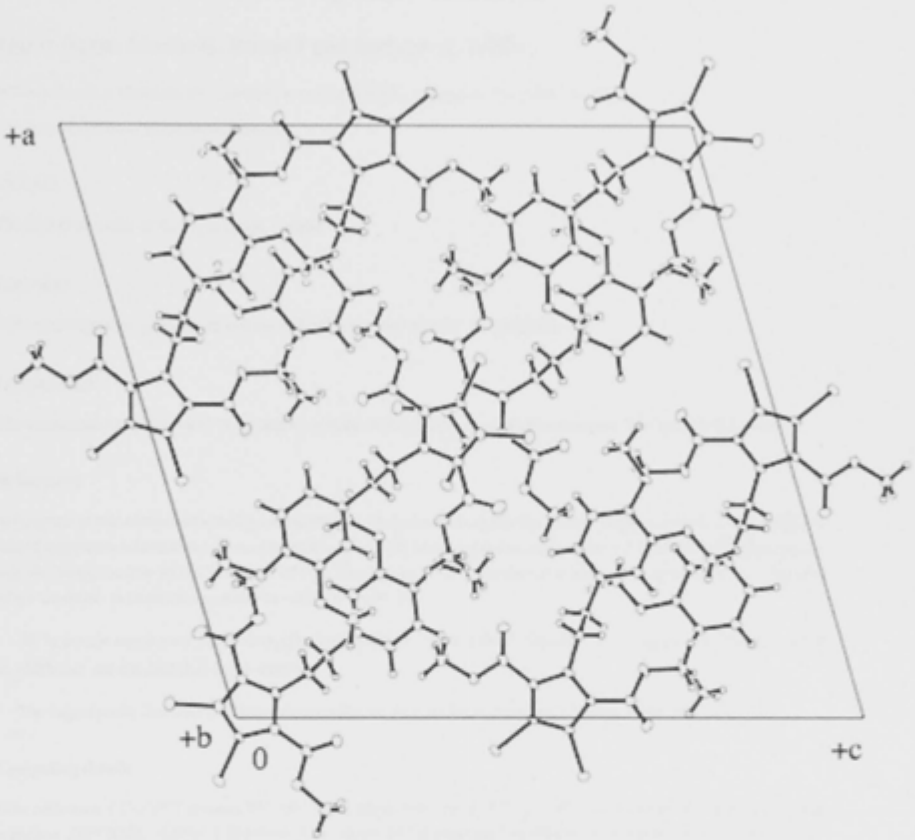


Figure 6.8. Unit cell packing diagram of $C_{18}H_{19}Br_2NO_6$ projected down the *b* axis. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Submitted to *Acta Cryst. C*

Crystal structure of $C_{18}H_{19}Br_2NO_6$ — ban0803a

Katrin Hasse, Martin G. Banwell and Anthony C. Willis

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: **willis@rsc.anu.edu.au**

Abstract

The crystal structure of $C_{18}H_{19}Br_2NO_6$ is reported.

Comment

The crystallographic asymmetric unit consists of two molecules of $C_{18}H_{19}Br_2NO_6$.

Experimental

The compound was prepared by KAA and recrystallized from chloroform/dichloromethane. The sample ID is kah247.

Refinement

All crystals of this compound which were examined were twinned. Examination of synthesized precession photographs revealed extra spots related to the indexed reflections by a 180° rotation about the reciprocal −1 0 1 direction. This relationship was also recognized by ROTAX within *CRYSTALS* and enabled the application of a twinning correction during refinement of the structure. Twin elements refined to 0.831 (2):0.169 (2).

All hydrogen atoms were included at calculated positions (C—H 1.00 Å, $U_{iso}(H) = 1.2 \times U_{eq}(C)$) and ride on the atom to which they are attached during refinement.

The largest peaks in a final difference electron density map are located near the Br atoms or along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEPII* (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0803a)

Crystal data

$C_{18}H_{13}Br_2NO_3$	$V = 3823.05\ (11)\ Å^3$
$M_r = 505.16$	$Z = 8$
Monoclinic, $P2_1/n$	Mo $K\alpha$
$a = 23.1353\ (4)$ Å	$\mu = 4.28\ mm^{-1}$
$b = 7.2938\ (1)$ Å	$T = 200$ K
$c = 23.6241\ (4)$ Å	$0.47 \times 0.23 \times 0.08$ mm
$\beta = 106.4603\ (7)^\circ$	

Data collection

Nonius KappaCCD diffractometer	6772 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	5599 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.318$, $T_{max} = 0.716$	$R_{int} = 0.079$
53713 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.055$	H-atom parameters not refined
$wR(F^2) = 0.166$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.09P)^2 + 22.05P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$S = 1.00$	$\Delta\rho_{max} = 0.81$ e Å^{-3}
6772 reflections	$\Delta\rho_{min} = -0.85$ e Å^{-3}
488 parameters	

Table 1
Selected geometric parameters (Å, °)

Br10—C3	1.873 (8)	N51—C55	1.392 (9)
Br11—C4	1.860 (7)	N51—C66	1.477 (9)
Br60—C53	1.878 (7)	C2—C3^{i}	1.377 (11)
Br61—C54	1.853 (6)	C2—C6	1.508 (11)
O7—C6	1.174 (11)	C3—C4	1.391 (11)
O8—C6	1.311 (10)	C4—C5	1.401 (10)
O8—C9	1.440 (10)	C5—C12	1.491 (11)
O13—C12	1.184 (9)	C16—C17	1.527 (10)
O14—C12	1.311 (9)	C17—C18	1.527 (9)
O14—C15	1.446 (11)	C18—C19	1.417 (10)
O24—C20	1.385 (9)	C18—C23	1.384 (11)
O24—C25	1.410 (10)	C19—C20	1.358 (11)
O26—C21	1.371 (8)	C20—C21	1.413 (11)
O26—C27	1.425 (10)	C21—C22	1.380 (10)

O57—C56	1.195 (10)	C22—C23	1.398 (10)
O58—C56	1.326 (9)	C52—C53	1.391 (9)
O58—C59	1.454 (9)	C52—C56	1.483 (10)
O63—C62	1.205 (9)	C53—C54	1.410 (10)
O64—C62	1.332 (8)	C54—C55	1.383 (10)
O64—C65	1.427 (9)	C55—C62	1.471 (10)
O74—C70	1.371 (8)	C66—C67	1.528 (9)
O74—C75	1.424 (10)	C67—C68	1.516 (10)
O76—C71	1.375 (8)	C68—C69	1.409 (10)
O76—C77	1.432 (9)	C68—C73	1.383 (11)
N1—C2	1.385 (10)	C69—C70	1.388 (10)
N1—C5	1.373 (10)	C70—C71	1.409 (11)
N1—C16	1.502 (9)	C71—C72	1.380 (11)
N51—C52	1.389 (9)	C72—C73	1.397 (11)
C6—O8—C9	116.0 (8)	O24—C20—C21	114.4 (6)
C12—O14—C15	115.7 (7)	C19—C20—C21	120.3 (7)
C20—O24—C25	117.7 (6)	C20—C21—O26	115.1 (6)
C21—O26—C27	117.9 (6)	C20—C21—C22	119.2 (6)
C56—O58—C59	115.8 (7)	O26—C21—C22	125.7 (7)
C62—O64—C65	117.1 (6)	C21—C22—C23	120.5 (7)
C70—O74—C75	117.4 (6)	C22—C23—C18	120.4 (7)
C71—O76—C77	117.1 (6)	N51—C52—C53	106.7 (6)
C2—N1—C5	109.4 (6)	N51—C52—C56	127.3 (6)
C2—N1—C16	126.0 (6)	C53—C52—C56	126.0 (7)
C5—N1—C16	124.6 (6)	Br60—C53—C52	127.1 (6)
C52—N51—C55	108.7 (5)	Br60—C53—C54	123.5 (5)
C52—N51—C66	126.5 (6)	C52—C53—C54	109.4 (6)
C55—N51—C66	124.8 (6)	Br61—C54—C53	124.0 (5)
N1—C2—C3	106.9 (6)	Br61—C54—C55	129.7 (5)
N1—C2—C6	127.0 (6)	C53—C54—C55	106.2 (6)
C3—C2—C6	126.1 (7)	N51—C55—C54	108.9 (6)
Br10—C3—C2	126.9 (6)	N51—C55—C62	122.3 (6)
Br10—C3—C4	123.7 (6)	C54—C55—C62	128.5 (6)
C2—C3—C4	109.2 (7)	C52—C56—O58	113.3 (7)
Br11—C4—C3	123.3 (6)	C52—C56—O57	122.4 (7)
Br11—C4—C5	129.6 (6)	O58—C56—O57	124.3 (7)
C3—C4—C5	106.8 (7)	C55—C62—O64	110.3 (6)
C4—C5—N1	107.6 (6)	C55—C62—O63	125.9 (6)
C4—C5—C12	128.9 (7)	O64—C62—O63	123.8 (7)
N1—C5—C12	123.3 (6)	N51—C66—C67	110.2 (6)
C2—C6—O8	113.3 (7)	C66—C67—C68	110.5 (6)
C2—C6—O7	121.1 (8)	C67—C68—C69	119.6 (7)
O8—C6—O7	125.6 (8)	C67—C68—C73	121.8 (7)
C5—C12—O14	109.8 (6)	C69—C68—C73	118.6 (6)
C5—C12—O13	125.4 (7)	C68—C69—C70	120.8 (7)
O14—C12—O13	124.9 (8)	C69—C70—O74	125.3 (7)
N1—C16—C17	109.5 (6)	C69—C70—C71	119.5 (6)
C16—C17—C18	109.6 (6)	O74—C70—C71	115.3 (6)
C17—C18—C19	120.8 (7)	C70—C71—O76	114.9 (6)

C17—C18—C23	120.6 (7)	C70—C71—C72	119.8 (7)
C19—C18—C23	118.6 (7)	O76—C71—C72	125.3 (7)
C18—C19—C20	121.0 (7)	C71—C72—C73	120.2 (7)
O24—C20—C19	125.3 (7)	C72—C73—C68	121.0 (7)

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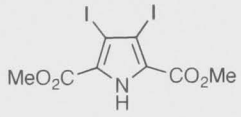
Dimethyl 3,4-diiodo-1*H*-pyrrole-2,5-dicarboxylate (101)



101

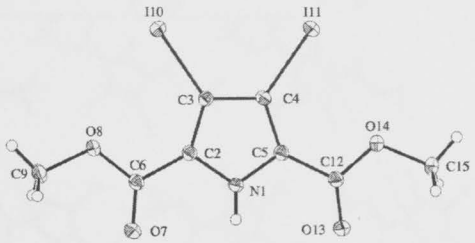


Figure 6.9. Molecular structure of $C_8H_7I_2NO_4$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

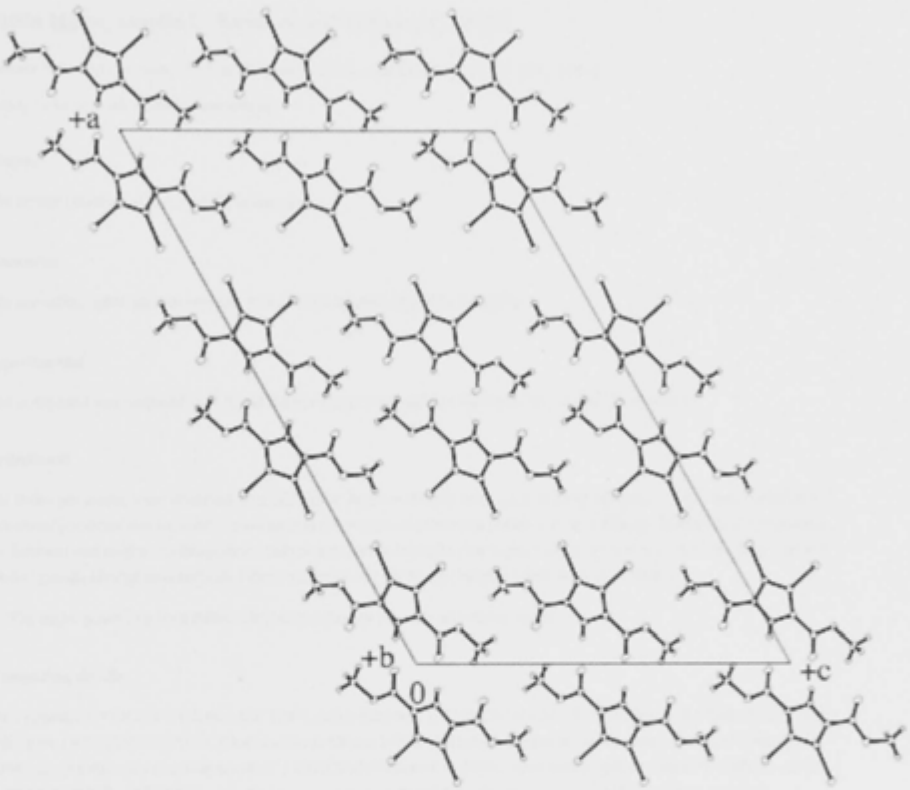


Figure 6.10. Unit cell packing diagram of $C_8H_7I_2NO_4$ projected down the *b* axis. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Crystal structure of $C_8H_7I_2NO_4$ — ban0816a

Katrin Hasse, Martin G. Banwell and Anthony C. Willis

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: willis@rsc.anu.edu.au

Abstract

The crystal structure of $C_8H_7I_2NO_4$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_8H_7I_2NO_4$.

Experimental

The compound was prepared by KH and recrystallized from dichloromethane. The sample ID is kah322.

Refinement

All hydrogen atoms were observed in a difference electron density map prior to their inclusion. They were included at calculated positions, and then their coordinates and isotropic displacement parameters were refined. Restraints were imposed on distances and angles involving them, and on their isotropic displacement parameters, without restraints the angles on the methyl groups diverge unacceptably from tetrahedral and the N—H distance tends to be very short.

The major peaks in a final difference electron density map are near iodine atoms.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZOSCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZOSCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEPII* (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0816a)

Crystal data

$C_8H_7I_2NO_4$	$V = 2218.41\ (10)\ Å^3$
$M_r = 434.96$	$Z = 8$

Monoclinic, $C2/c$	Mo $K\alpha$
a = 31.2344 (8) Å	μ = 5.66 mm^{-1}
b = 4.2399 (1) Å	T = 200 K
c = 19.1462 (5) Å	0.36 × 0.10 × 0.07 mm
β = 118.9638 (11)°	

Data collection

Nonius KappaCCD diffractometer	2526 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	2107 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.310, T_{max} = 0.690	R_{int} = 0.044
20539 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.019	32 restraints
$wR(F^2)$ = 0.053	All H-atom parameters refined
S = 0.92	$\Delta\rho_{max}$ = 0.73 e Å^{-3}
2526 reflections	$\Delta\rho_{min}$ = −0.74 e Å^{-3}
164 parameters	

Table 1
Selected geometric parameters (Å, °)

N1—C2	1.363 (4)	C5—C12	1.475 (4)
N1—C5	1.361 (4)	C6—O7	1.195 (4)
C2—C3	1.384 (4)	C6—O8	1.330 (4)
C2—C6	1.474 (4)	O8—C9	1.452 (3)
C3—C4	1.409 (4)	C12—O13	1.197 (4)
C3—I10	2.065 (3)	C12—O14	1.326 (4)
C4—C5	1.396 (4)	O14—C15	1.443 (4)
C4—I11	2.056 (3)		
C2—N1—C5	110.0 (2)	C4—C5—C12	133.8 (3)
N1—C2—C3	107.9 (2)	N1—C5—C12	118.6 (2)
N1—C2—C6	117.0 (2)	C2—C6—O7	122.9 (3)
C3—C2—C6	135.1 (3)	C2—C6—O8	112.9 (2)
C2—C3—C4	107.4 (2)	O7—C6—O8	124.2 (3)
C2—C3—I10	128.7 (2)	C6—O8—C9	115.9 (2)
C4—C3—I10	123.6 (2)	C5—C12—O13	123.0 (3)
C3—C4—C5	107.0 (2)	C5—C12—O14	112.6 (2)
C3—C4—I11	125.3 (2)	O13—C12—O14	124.3 (3)
C5—C4—I11	127.7 (2)	C12—O14—C15	115.9 (2)
C4—C5—N1	107.6 (2)		

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